Library (Scientific Research) Section

President F C Kelly PhD

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President's Address

Iodine in Medicine and Pharmacy Since its Discovery—1811-1961

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To compress into one brief hour the whole medical history of iodine since its discovery by the French chemist, Bernard Courtois, one hundred and fifty years ago, is manifestly impossible. I propose, therefore, to follow only one or two of the more important threads that make-up the warp and woof of what for me has always been a fascinating story.

Like so many other scientific advances, the discovery of iodine was a discovery quickened under the urgency and pressure of war. At the beginning of the nineteenth century, France, obedient to the dictates of Napoleon's ambitious dreams, was fighting with almost all her neighbours and she needed enormous quantities of gunpowder to do the job. Hemmed-in on land by the armies of Prussia and Austria, and blockaded at sea by the British Navy, her supplies of chemicals necessary for the manufacture of gunpowder were cut off. One of these chemical essentials was saltpetre – nitrate. What did France do? As she was unable to get nitrate from beyond her borders, she made it at home, artificially, in specially constructed nitre beds. And it was while engaged in the manufacture of saltpetre on one of these artificial 'nitre plantations', near Paris, that Bernard Courtois made his discovery.

The story has often been told. The key-point is that to make saltpetre you must have a plentiful supply of soda. Courtois obtained his soda from the ashes of seaweed – called variously *varec*, *varech*, or *vareck* in French, and *wrack* or, more commonly, *kelp* in English. Extraction of the soluble sodium carbonate from the seaweed ash was carried out in metal vats, and after successive extractions there remained at the bottom of the vessels a thick mother liquor encrusted with insoluble material.

From time to time it was necessary to clean out these deposits with the aid of acid and heat. It seems that one day Courtois added stronger acid than usual, for he was astonished to see intensely beautiful violet-coloured vapours arising from the mixture. He noticed, furthermore, that these vapours formed a deposit of lustrous metal-like crystals on the cooler parts of the vessel.

Here was a new and strange phenomenon. His curiosity aroused, Courtois scraped off some of the mysterious substance, and, by a brief examination, determined its more obvious chemical properties. But he was far too busy with the management of his saltpetre factory to carry his investigations very far; so he gave specimens of the new product to his closest professional friends asking them to continue the study where he had left off. Among those who received specimens were Gay-Lussac, the most distinguished French chemist of his day, and also Ampère.

Now, all this happened towards the end of the year 1811 – probably in the month of November – the exact date of the discovery of iodine is not known.

Two years elapsed.

On October 27, 1813, there arrived in Paris from England a remarkable quartette. They were: Sir Humphry Davy, the eminent English chemist; his temperamentally unpredictable wife, Lady Davy; her lady's maid; and Davy's assistant and valet, none other than Michael Faraday, then an obscure young man of 22, who was eventually to become more famous than his master.

Remember that England was then at war with France; but in those days wars were solely the affair of soldiers and sailors; men of science continued to correspond with each other and remained constantly on good terms. So it was that when Davy expressed a desire to pass through France on a journey to Italy, Napoleon, always an ardent patron of science, immediately ordered that passports be issued.

Among the first to greet Davy on his arrival in Paris was Ampère who, in an eager and generous moment, gave Davy a sample of the unknown 'X', as they called it. Davy got to work upon it and soon satisfied himself that it was a new elementary

substance analogous to chlorine. On tour, Davy always carried a compact travelling laboratory around with him – a 'chemistry set' we would call it nowadays.

Gay-Lussac – Davy's only professional equal in France, or indeed anywhere else – was furious when he heard what Ampère had done. His irritation is understandable. He was annoyed, not so much with Ampère, as with himself for being so slow. After all, he had had substance 'X' in his hands for two years and had already proved its elementary nature; but alas, had published nothing.

There followed an undignified scramble into print to establish priority, and a bitter 'priority' quarrel broke out between Davy and Gay-Lussac. The details need not detain us; they are well documented.

For posterity, the happy outcome of these controversial days was the birth of a new and beautiful element. Its name, given by Gay-Lussac in French – 'iode' – and anglicized by Davy – 'iodine' – is derived, like so many of the loveliest words in English, from the Greek – from the word ἰοειδής meaning 'violet coloured'.

From Folk Medicine to Rational Therapy

Comparatively soon after its discovery, iodine found favour as a therapeutic agent – a medicine.

Looking backwards from the precarious heights of 1961 down through the past century and a half, we can discern two distinct lines of advance which could not, of course, be foreseen by those who launched iodine upon its medical and pharmaceutical career.

The first illustrates perfectly how, as medical science progresses, the unexplained virtues of a traditional remedy – some part of folk medicine, let us say – become wholly intelligible when exposed to the light of exact biological knowledge.

In 1656, more than one hundred and fifty years before the discovery of iodine, a London physician called Thomas Wharton described and named a gland in the neck: he called it the *thyroid* gland – the shield-shaped gland. He says: 'It contributes much to the beauty of the neck, filling-up the vacant spaces around the larynx, making its protuberant parts smooth, particularly in females, to whom for this reason a larger gland has been assigned, which renders their necks more even, and more beautiful.' Unhappily, thyroid glands do not always retain these delicate proportions. They sometimes get out of gear inside, and grow into the large unsightly swellings that we describe under the general term of goitre.

Goitre has troubled mankind from time immemorial; and from time immemorial man has sought to overcome it. Centuries before the discovery of iodine, the most highly-prized remedy for goitre was a concoction containing the ashes of burnt sea sponge. Some say that this remedy originated in the very early medical experience of China, where goitre then abounded and indeed still abounds. Certainly the burnt-sponge remedy was known to European medicine in the Middle Ages (thirteenth century, let us say) and eventually found its way to England, where, in the mid-1700s, burnt sponge was famed as the 'Coventry Remedy'.

For many a year, the Coventry recipe was held secret by the family of a Dr Bate of that town. They administered it with such success as to gain them a wide reputation and no small fortune. Only in 1779 was it disclosed that the essential ingredient was burnt sponge.

Now, in 1819, eight years after the discovery of iodine, Andrew Fyfe, then lecturer in chemistry at the University of Edinburgh, found that the common sea sponge always contains exceptionally high quantities of iodine. Although Fyfe did not realize it, his discovery was important because it provided a link in the chain of evidence that proved iodine to be the active curative principle in burnt sponge.

In the same year (1819) a prominent physician in Geneva, Jean François Coindet, ignorant of Fyfe's findings, but aware of the virtues of burnt sponge and of seaweed ash as remedies for goitre, suspected that iodine, discovered in seaweed but a few years earlier, might be the active therapeutic agent common to these two marine products.

Coindet's test of this hypothesis met with dramatic success. By giving tincture of iodine to goitre patients – there were plenty of them in Switzerland, his native country – he could appreciably reduce large goitrous swellings within a week. So spectacular were his results, that everywhere they gained a wide publicity, and Coindet is generally regarded as having been the first to introduce iodine into medical practice in this way.

Claims for this honour have also been advanced by the celebrated English physician and chemist, William Prout, who stated (in 1834) that he first employed potassium iodide as a remedy for goitre in 1816. He says, also, that he told Dr John Elliotson about it, and that Elliotson commonly prescribed potassium iodide at St Thomas's Hospital as early as 1819.

Although these claims cannot be verified in any contemporary record, there is no reason to doubt them. Incidentally, Dr Elliotson was the first President of this Society after its incorporation as the Royal Medical and Chirurgical Society of London in 1834; his name appears in our first Charter, and there is a good portrait of him in the Council chamber on the 4th floor.

Hard on the heels of Coindet's remarkable therapeutic results came the suggestion that the cause of goitre is a lack of iodine in the system

brought about by a deficiency of the element in water, soil, and food. Credit for this belongs to the French chemist, Gaspard Adolphe Chatin who, between the years 1850 and 1876, found that the iodine content of waters, and of foodstuffs of vegetable origin grown in goitre areas, was less than that in healthy areas.

Unfortunately, Chatin's conclusions failed to convince his contemporaries, and his attempt to establish a causal relationship between environmental iodine deficiency and the occurrence of endemic goitre lay neglected and forgotten until the end of the nineteenth century.

To-day, the opinions of Coindet and of Chatin stand completely justified. First step in their vindication was the fundamental discovery in 1895, by the German chemist Baumann, that iodine is an invariable constituent of the normal thyroid gland. This at once gave point to the iodine treatment of goitre introduced by Coindet seventy-five years earlier. Next major advance resulted from investigations carried out between the years 1913 and 1919 by E C Kendall at the Mayo Foundation, Rochester, N.Y., who was the first to isolate the iodine-containing hormone of the thyroid gland in crystalline form. He named it 'thyroxine'. Then came the notable work of Sir Charles Harington, around the years 1925 to 1930, who determined the exact chemical constitution of thyroxine, proved that the molecule contains four atoms of iodine, devised means for its artificial synthesis, and drew attention to the principal chemical features responsible for its specific physiological activity.

'It is interesting to reflect', writes Sir Charles, 'that even if we date the first therapeutic use of burnt sponge from the middle of the thirteenth century, this remedy was known as a specific for thyroid disease some five hundred and fifty years before the discovery of the element to which it owed its activity, and some six hundred and fifty years before the final demonstration of the role of the element in the economy of the thyroid gland itself.'

This gradually unfolding knowledge brought a new outlook on the whole question of local iodine deficiency as a cause of goitre. Soils, foods, and drinking-waters from goitrous and non-goitrous regions have been examined afresh by refined modern techniques, and the results amply confirm Chatin's dictum that where iodine is scarce – either in absolute or relative terms – there also will you find goitre.

Through the enlightened efforts of the World Health Organization goitre surveys have been carried out all over the world in recent years and we now have 18 major countries where, by law, all kitchen and table salt is iodized in the interests of public health. Twenty others, hesitant to impose legal compulsion, nevertheless officially encourage the community use of iodized salt as a preventive measure in the public interest.

After all, according to best estimates, there are in the world to-day 200 million people who suffer from thyroid deficiency in greater or lesser degree.

I would mention here that iodization of salt to prevent goitre is no new-fangled notion. It was first recommended one hundred and thirty years ago, in 1831, by that delightful character, J B Boussingault – mining engineer, chemist, agronomist, traveller, *bon vivant* – probably the most peripatetic scientific Frenchman of his day who, on his travels in South America, noticed that the natural salt deposits, instinctively preferred by the peoples of goitrous districts in Colombia, contained most iodine.

General Therapy

But enough of iodine-deficiency goitre; let us move to another chapter in the iodine story – the ups and downs in its career as a general therapeutic agent, and as antiseptic and disinfectant.

Around the time iodine was discovered, French medicine was in the ascendant; traditional methods – bleeding, purging, the leech – were on the way out and yielding place to the first beginnings of experimental pharmacology. Pioneer in this new movement was François Magendie then at the height of his fame as an experimentalist. He it was who first put iodine into a pharmacopœia – in the year 1821.

In the first flush of enthusiasm for the newcomer, physicians and surgeons tested it and tried it for every conceivable pathological condition. The variety of diseases for which iodine was prescribed in the early years is astonishing – paralysis, chorea, scrofula, lacrimal fistula, deafness, distortions of the spine, hip-joint disease, syphilis, acute inflammation, gout, gangrene, dropsy, carbuncles, whitlow, chilblains, burns, scalds, lupus, croup, catarrh, asthma, ulcers, and bronchitis – to mention only a few.

Indeed, tincture of iodine, iodoform, or one of the iodides, was applied to almost every case that resisted the ordinary routine of practice; and between 1820 and 1840 there appeared a remarkable series of essays and monographs testifying to the extraordinary benefits to be achieved by this new and potent remedy.

In the Great Exhibition at the Crystal Palace in Hyde Park in May 1851 iodine and iodine compounds were publicly shown for the first time by ten pharmaceutical firms, including Hopkin and Williams of London, and Howards of Ilford – both still going strong.

Iodine preparations were urged and accepted into the prescribers' manuals of the day in rapidly increasing numbers. The first British Pharma-

copœia (1864) made a rigid selection of 14 preparations; by 1890, to choose a date at random, the 6th edition of Martindale's Extra Pharmacopœia sponsored 30 medicaments derived from iodine; the 'Iodine Centenary Volume' compiled by 'The Prescriber' in 1914 mentions 45 iodine preparations; by 1928 'Martindale' had extended its coverage to 128 iodine items; and, in an International Index published in 1956, and devoted exclusively to iodine pharmaceuticals, no less than 1,700 approved pharmacopœial names, proprietary names, synonyms, and alternative designations are alphabetically listed.

In the beginning, methods of applying iodine were scarcely less numerous than the variety of preparations available. The element was administered as vapour; as nascent iodine; in baths; in pills; in sweets; by inhalations; by irrigation, ionization and electrophoresis; in cigarettes; in tobacco, soaps, snuff, medicated matches, ointments, creams, hair-tonics, dusting-powders, suppositories, plasters, contraceptives, and even in an abortifacient.

Pharmaceutical literature of the nineteenth century is studded with iodine eponyms –Bryant's sherry; Churchill's caustic; Lugol's solution; Mandl's paint; Morton's fluid; Nourry's wine; Vanier's syrup; Whitehead's varnish – and so on. These men gave their names to the particular iodine preparations they invented and found useful. In French hospitals it was common practice to hang-up, on the crossbeams of the wards, strips of gauze steeped in iodoform (for all the world like old-fashioned fly-papers); and, in one Paris infirmary, the ward floors were strewn with dried seaweed in the belief that iodine emanations would pervade the atmosphere with beneficial effect.

Within a very short time of iodine's entry into medicine around 1820, ordinary people like ourselves, doubtless encouraged by the patent medicine vendors of the day, took to carrying little bottles of iodine hung round their necks, like amulets to charm away disease. Later, this practice fell into disrepute; but, oddly enough, was revived even in our own day.

Antiseptic and Disinfectant

First specific reference to the use of tincture of iodine in wounds appears to be that made in 1839 by John Davies, Surgeon to the General Infirmary, Hertford, whose 'Textbook on Surgery' included a special section on the application of tincture of iodine to lacerated, contused and punctured wounds. He did this, he says, 'to bring into general notice a remedy whose superior curative properties, as an external application, appear to be but little known to the Profession'.

The earliest recorded account of iodine tincture being applied to war wounds – wounds sustained on the battle-field – relates to the American Civil War.

On September 29, 1862, Colonel John B Gordon held the centre of General Lee's army at the battle of Antietam, or Sharpsburg. The first volley from the northern lines sent a ball through the calf of Gordon's right leg; soon after, another went through the muscles of his thigh; a third pierced his left arm, tearing asunder the tendons and mangling the flesh; a fourth ripped through his shoulder leaving a wad of clothing embedded in its track. Still, no bones were broken; but, while Gordon lingered in the firing line, 'with', as he says himself, 'but little of my usual strength', a fifth ball struck him squarely in the face.

Dr Weatherly of the 6th Alabama Regiment, in charge of medical arrangements, had the Colonel removed to a base hospital, and prescribed tincture of iodine to be painted on the wounds three or four times a day. The case was unpromising. Gordon's eyelids were greatly swollen; one eye was completely closed, the other almost so; his jaw was immovably clenched, and, to make matters worse, erysipelas had set in on the left arm.

Mrs Gordon, his wife, who nursed him – her name was Fanny, and she was then a beautiful girl of 25 – put a liberal interpretation on her instructions and painted the wounds, not three or four times a day, but, as Gordon himself says: 'I think three or four hundred times a day.' Fanny's diligence and devotion were rewarded. Her husband survived, outlived the war, became Governor of Georgia, a General, and Commander-in-Chief of the United Confederate Veterans. He died in 1904.

And so it came about that in every war throughout the remainder of the century, and indeed until the end of the 1914–1918 war, iodine tincture was declared a requisite in all field hospital stores and pharmacy waggons. Those of you who are old enough will remember the 'first field dressing' of 1914–1918, tucked into a little pocket on the left-hand inner-side corner of the battle tunic. It may fairly be said that at the beginning of the First World War most surgeons felt secure in the belief that a prompt application of a solution of iodine in spirit would suffice for the primary disinfection of a wound of moderate size; and that was why a small capsule of 2% tincture of iodine was included along with gauze and safety-pins in the 'first field dressing'.

Unhappily, the field conditions under which that war was waged inevitably gave rise to grossly infected wounds against which no chemical antiseptic was of any avail whatever, unless applied in excessive strength damaging to the living tissue. The technical reasons for this failure of iodine to

SOME LANDMARKS IN THE MEDICAL HISTORY OF IODINE

IODINE IN THE BRITISH PHARMACOPOEIA

	MONOGRAPHS	1st 1864	2nd 1867	3rd 1885	4th 1898	5th 1914	6th 1932	7th 1948	8th 1953	9th 1958	Addm. 1960
INORGANIC IODINE	ARSENIC IODIDE									Dermatology	
	CADMIUM IODIDE									Dermatology	
	HYDRIODIC ACID									Expectorant	
	IODINE									The Parent Substance	
	AQUEOUS IODINE SOLUTION									Lugol's Panacea	
	SIMPLE IODINE SOLUTION									Anti-Rheumatic	
	STRONG IODINE SOLUTION									Antiseptic and Disinfectant	
	WEAK IODINE SOLUTION									Antiseptic and Disinfectant	
	IODINE OINTMENT									Counter Irritant	
	IODINE VAPOUR									Respiratory Disease	
	IRON IODIDE									Tonic and Alterative	
	IRON IODIDE SYRUP									Tonic	
	LEAD IODIDE									Dermatology	
	MERCURY IODIDE, GREEN									Antisyphilitic	
	MERCURY IODIDE, RED									Antisyphilitic	
	POTASSIUM IODIDE									Alterative; Antisyphilitic; Expectorant; Diuretic; Etc.	
	SODIUM IODIDE									Alterative; Antisyphilitic; Etc.	
	SULPHUR IODIDE									Dermatology	
ORGANIC IODINE	CHINIOFON									Amoebicide	
	DECAMETHONIUM IODIDE									Anaesthesia	
	DI-IODOHYDROXYQUINOLINE									Amoebicide	
	DIODONE									Contrast Medium	
	EMETINE BISMUTH IODIDE									Amoebicide	
	GALLAMINE TRIETHIODIDE									Anaesthesia	
	IODOFORM									Antiseptic	
	IODOPHTHALEIN									Contrast Medium	
	IODOXYL									Contrast Medium	
	IOPANOIC ACID									Contrast Medium	
	LIOTHYRONINE, SODIUM									Thyroid Hormone	
	PHENIODOL									Contrast Medium	
	PROPYLIODONE									Contrast Medium	
	THYROID, DRIED									Thyroid Hormone	
	THYROXINE, SODIUM									Thyroid Hormone	

Table 1

FROM FOLK MEDICINE
to
RATIONAL THERAPY

4th to 8th Century A.D.	**INFUSION OF SEAWEED** used to treat thyroid enlargement (goitre) by Chinese physician KE-HUNG (281-361). WANG T'AO (8th Century) lists 36 goitre prescriptions, 27 of which contain preparations of seaweed or other marine product.
1779	**COVENTRY REMEDY.** A secret remedy for goitre, now known to have contained "calcined spunge" brought a wide reputation and no small fortune to its owners, a doctor and an apothecary in Coventry. Details were published in 1779..
1811	**DISCOVERY OF "A NEW SUBSTANCE"** in seaweed ash by BERNARD COURTOIS (1777-1838). Not announced until 1813.
1813 27 Oct.	**ARRIVAL** of HUMPHRY DAVY (1778-1829) in Paris *en route* to Italy. Given a sample of the new substance; submitted it to experiment and "soon satisfied himself that it was a new elementary body analogous to chlorine."
1813 29 Nov.	**FIRST PUBLIC ANNOUNCEMENT** of COURTOIS' discovery made by C. B. DESÓRMES (1777-1862) and N. CLÉMENT (1779-1841) at meeting of Imperial Institute of France.
1813 6 Dec.	**NAMING OF IODINE.** J. L. GAY-LUSSAC (1778-1850) made known the results of *his* preliminary experiments, claimed the substance to be a new element and named it *Iode*.
1813 10 & 11 Dec.	**CONTROVERSY.** From Paris, HUMPHRY DAVY sent communications to The Royal Society of London and to the Imperial Institute of France seeking to establish that he, not GAY-LUSSAC, was the the first to prove iodine an element.
1816	**FIRST MEDICAL USE?** Writing in 1834, WILLIAM PROUT, M.D., F.R.S. (1785-1850) claims that he first used potassium iodide as a remedy for goitre in 1816.
1816	**DISCOVERY IN SPONGES.** ANDREW FYFE, M.D. (1792-1861), lecturer in chemistry, Edinburgh University and later professor of medicine and of chemistry at King's College, Aberdeen, demonstrated that iodine is a normal constituent of the common sponge.
1819	**TINCTURE A GOITRE SPECIFIC.** J. F. COINDET, M.D. (1774-1834) of Geneva, announced in 1820 to the Swiss Society of Natural Sciences his discovery, a year previously, that iodine tincture is a specific for goitre. COINDET is generally regarded as having been the first to introduce iodine into medical practice.

1819 SAINT THOMAS'S HOSPITAL. JOHN ELLIOTSON*, M.D., F.R.S. (1786-1868). Adopted potassium iodide as a remedy for goitre at St. Thomas's Hospital on the suggestion of Prout (*q.v.* 1816).

1831 IODIZED SALT FIRST RECOMMENDED. J. B. BOUSSINGAULT (1802-1887) noticed in 1825 that local salt supplies instinctively preferred by the inhabitants of goitrous districts in Colombia contained most iodine. He therefore recommended the iodization of cooking salt for goitre prevention.

1838 VIRTUE IN HARROGATE WATERS. *Dr.* JAMES INGLIS observed that goitre was common in the country around Harrogate but rare in the town itself. He ascribed this immunity to the presence of iodine and bromine in the Harrogate water.

1846 IODINE DEFICIENCY THEORY. Arguing from the successful therapeutic results obtained by COINDET (*q.v.* 1819) with iodine, J. L. PRÉVOST (1790-1850) of Geneva, in collaboration with his Italian colleague A. C. MAFFONI (1806-1878) first suggested that a deficiency of this very element in drinking water is the cause of simple endemic goitre.

1850 to 1876 FIRST CHEMICAL PROOF, by the French analyst G. A. CHATIN (1813-1901), that deficiency of iodine in air, water, soil and food is the primary cause of endemic goitre.

1895 DISCOVERY IN THYROID. Fundamental discovery that iodine is an invariable constituent of the normal thyroid gland was made by E. A. G. BAUMANN of Freiburg.

1913 to 1919 ISOLATION OF THYROID IODINE HORMONE. The iodine-containing principle of the thyroid gland was first isolated in crystalline form by E. C. KENDALL, M.D., Rochester, who showed it to contain 65 per cent of iodine, and named it *Thyroxine*.

1925 to 1930 SYNTHESIS OF THYROXINE. CHARLES R. HARINGTON, F.R.S., determined the chemical constitution of *Thyroxine* to be tetra-iodothyronine, devised means for its artificial synthesis, and pointed out the principal chemical features responsible for its specific physiological activity.

1952 TRIIODOTHYRONINE. Discovery by JACK GROSS and ROSALIND PITT-RIVERS that *Triiodothyronine* is present in the thyroid gland and forms a proportion of the circulating hormone, marks a new forward step towards eventual elucidation of precise chemical and physiological purpose of iodine within the animal body.

* *First President of the Royal Society of Medicine after its incorporation by Royal Charter in* 1834.

1. J. G. A. Lugol (1786-1851) originator of the aqueous solution of iodine (with KI) for treating scrofula.

2. Humphry Davy (1778-1829) wrote the first account of iodine in English.

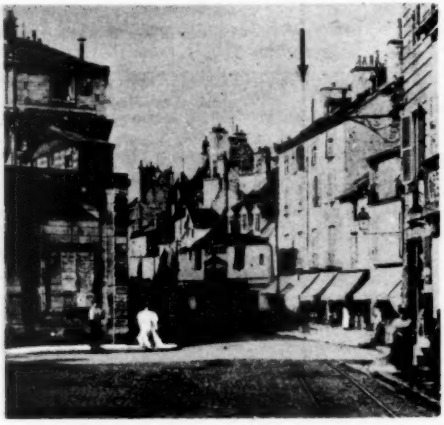
3. Gaspard Adolphe Chatin (1813-1901) first to show that deficiency of iodine in air, water and soil is associated with the occurrence of endemic goitre.

4. Eugen Baumann (1846-1896) discovered that iodine is an invariable constituent of the normal thyroid gland.

5. Thomas Wharton (1614-1673) described and named the thyroid gland in 1656.

6. Jean-François Coindet (1774-1834) introduced tincture of iodine as a goitre specific in 1819.

7. J. L. Gay-Lussac (1778-1850) proved iodine to be an element and named it.



8. The house in Dijon where Bernard Courtois was born.

(Photographs 1, 5, 7 reproduced by courtesy of the Wellcome Historical Medical Museum, London)

MATERIA MEDICA

1821 MAGENDIE'S FORMULARY. Iodine included for the first time in a prescribers' manual—the *Formulary* of FRANÇOIS MAGENDIE (1783-1855).

1821 IODINE TINCTURE INTRODUCED TO ENGLAND. *Sir* ANDREW HALLIDAY, M.D. (1781-1839) first to make detailed recommendations to the medical profession in England of the therapeutic uses and advantages of iodine preparations (especially the tincture) for diseases other than goitre.

1822 IODOFORM discovered by the French chemist, SÉRULLAS. Arguments for and against its medical efficacy continued throughout the 19th Century.

1829 INHALATIONS OF IODINE VAPOUR first recommended by *Sir* JAMES MURRAY, M.D. (1788-1871) for consumption, croup, catarrh, asthma and other respiratory diseases.

1829 LUGOL'S SOLUTION. J. G. A. LUGOL (1786-1851), physician in the Hospital of St. Louis, Paris, introduced the aqueous solution of iodine (with KI) for the treatment of "les maladies scrofuleuses". Wrote three memoirs on the subject.

1839 WOUNDS. First specific reference to the use of tincture of iodine in *wounds* made by JOHN DAVIES, surgeon, Hertford.

1851 POLAROID. WILLIAM B. HERAPATH, M.D. (1796-1868), professor of chemistry at Bristol Medical School, discovered that iodoquinine sulphate ("Herapathite") has light-polarizing properties. Forerunner of the modern *Polaroid*.

1862 BATTLEWOUNDS. Earliest recorded account of iodine tincture applied to wounds *sustained in battle* (American Civil War).

1864 IODINE finds a place in the 1st British Pharmacopoeia as *Linimentum Iodi* and *Tinctura Iodi*.

1865 ANTISEPTIC. A. A. BOINET, French surgeon, published his classic, *Iodothérapie*, in which he describes iodine as "un antiseptique, un désinfectant précieux."

1873 GERMICIDE. C. J. DAVAINE, French bacteriologist; first *knowingly* to employ iodine tincture as an agent for the destruction of infective organisms (anthrax).

1881 ROBERT KOCH (1843-1910). By common consent the greatest pure bacteriologist of his era. First to emphasize the germicidal potency of *aqueous* iodine solution.

1902 CATGUT STERILIZATION. M. CLAUDIUS, Danish bacteriologist, inaugurated a new safety era in surgery by recommending aqueous solution of iodine for the sterilization of surgical sutures. Aqueous iodine remains today the only effective *chemical* disinfectant of raw catgut.

1908 SKIN DISINFECTION. German surgeon, A. GROSSICH, was first to define and apply a rigid technique—known as the *Grossich technique*—for pre-operative skin sterilization by means of iodine tincture.

1910 "BRYANT'S SHERRY." Synonym for tincture of iodine. London surgeon THOMAS BRYANT* (1828-1914) wrote in 1910: "After 40 years experience I am pleased to express an opinion that it [iodine] is without doubt the best antiseptic that surgeons of the present day possess."

1916 "BIPP". RUTHERFORD MORISON, F.R.C.S. (1853-1939), famous Newcastle surgeon, originated *Bipp* (bismuth iodoform paraffin paste). "In *Bipp* we have discovered an antidote to true sepsis, and can leave dirty wounds undressed for a whole month."

1919 TRANSITION. ALEXANDER FLEMING (1881-1955) by exhaustive experiments at St. Mary's Hospital, London, in collaboration with *Sir* ALMROTH WRIGHT, proved conclusively that disinfection of an already infected wound by any then known chemical disinfectant (iodine among them) is not possible except at a strength destructive to body tissues. Ten years later (1929) *Sir* ALEXANDER FLEMING, F.R.S., discovered the first antibiotic, *Penicillin*, which virtually eclipsed purely chemical methods of disinfecting blood and body tissues.

1921 CONTRAST MEDIA. Advent of iodized poppyseed oil, first radio-opaque iodine contrast medium. Today (1961) iodo-contrast media account for more than 150 tons of iodine annually.

1939 END OF AN ERA. Last and perhaps greatest protagonist of direct energetic iodine disinfection of wounds was *Sir* LEONARD ERSKINE HILL, F.R.S. (1866-1952) director of research, St. John Clinic and Institute of Physical Medicine, London. Convinced iodine veteran of World War I, he returned to its defence on outbreak of World War II, extolling virtues of intensive iodine disinfection of wounds "in all their depths and ramifications". Views not accepted by the moderns. With him died finally the 1914-1918 war faith in the iodine "first field dressing."

1949 IODOPHORS. Iodine tamed. HERMAN SHELANSKI, M.D., of Philadelphia discovered that polyvinyl pyrrolidone and various surfactants solubilize iodine to form highly active complexes which do not sting or stain.

* *President of the Royal Society of Medicine*, 1898.

WORLD CONSUMPTION OF IODINE BY SOURCE OF PRODUCTION

YEAR	EPISODE	SOURCE	WORLD CONSUMPTION OF IODINE (10-year averages, excluding USSR.)				
			DECADE	SEAWEED	CALICHE	WATERS	TOTAL
					(METRIC TONS)		
1811	BERNARD COURTOIS: discovers Iodine in the ashes of	Seaweed					
1820-40	FRANCE, sole world producer	Seaweed					
1840	HAYES discovers Iodine in Chilean	Caliche	1840/49	31			31
1841	SCOTLAND begins production	Seaweed					
1855	JACQUELAIN: 1st extraction from Chilean	Caliche	1850/59	65			65
1860	IRELAND begins production	Seaweed	1860/69	90	1		91
1868	CHILE: first export of Iodine	Caliche					
1879	NORWAY begins production	Seaweed	1870/79	92	26		118
1888	JAPAN begins production	Seaweed	1880/89	72	164		236
1892	JAVA begins production	Waters	1890/99	100	345	2	447
1900	SOUTH AFRICAN WAR (1899-02)		1900/09	186	346	11	543
1914	WORLD WAR I (1914-18)		1910/19	200	627	31	858
1926	U.S.A. begins production	Waters	1920/29	177	626	53	856
1927	ITALY begins production	Waters					
1933	JAPAN begins production	Waters	1930/39	146	632	229	1007
1934	IRELAND and NORWAY cease production from Seaweed						
1936	SCOTLAND ceases production from Seaweed						
1938	JAPAN ceases production from Seaweed						
1939	WORLD WAR II (1939-1945)						
1940	JAVA ceases production from Waters		1940/49	42	889	348	1279
1950-59	CHILE, JAPAN, U.S.A., ITALY, sole	Caliche &	1950/59		1068	735	1803
1960-	producers today (excluding USSR.)	Waters	1960		1200	800	>2000

Table 2

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live up to preconceived ideas were exposed, at St Mary's Hospital, in classic experiments by Sir Almroth Wright and Alexander Fleming (later Sir Alexander Fleming of penicillin fame). And, as a result, iodine was withdrawn from the 'first field dressing' and from all official procedures by which wounds were treated in the Navy, Army and Air Force.

On the outbreak of the Second World War in 1939, one or two redoubtable diehards – I cannot but admire their tenacity – sprang to a renewed defence of iodine for swabbing wounds 'in all their depths and ramifications'. These efforts, however, did nothing to influence the contemporary outlook. All they did was to mark the end of what I call the energetic era of wound management.

To-day, there are only three major disinfectant roles for which iodine is fitted – and for which it has no equal. These are: rapid disinfection of unwashed intact skin; the sterilization of surgical catgut (iodine is the only chemical that will do this infallibly); and, thirdly, the emergency sterilization of infected drinking water.

Contrast Media

An entirely new chapter in the medical fortunes of iodine opened with the discovery of X-rays in 1895 – a development that put a new diagnostic aid into the hands of physicians, and brought undoubted advantage to iodine producers and pharmaceutical manufacturers alike.

Soon after their discovery, the suggestion was made that substances through which X-rays cannot pass might be introduced into the body to provide contrast shadows and so make organs and tissues visible on a radiographic film.

Iodine is a substance endowed with the power to stop X-rays. Moreover, it has other attributes desirable in the make-up of contrast media as they are called. The year 1921 saw the first contrast medium in use – an iodized oil named Lipiodol. By introducing a little of this into the lungs and air cavities, and then applying the X-ray, a shadow picture of the bronchial tree is obtained from which experts can readily determine whether all is well or something wrong.

Brain, arteries, the veins, kidneys, liver, gallbladder, the reproductive organs, and almost every other bodily structure may be examined in this way. To-day, about 30 basic iodo-contrast media are available. But by the requirements of pharmacy firms, these same 30 are sold under something like 200 different proprietary brands and designations.

Chemotherapy

The turn of the century also saw the birth of a new chemistry – biochemistry – which brought with it the gradual ascendancy of rational over empirical modes of treatment. Broadly speaking, chemotherapy, or replacement therapy, is the intelligent use against disease of these very drugs, extracts and principles which the living body continually manufactures within itself to keep itself alive, and whose deficiency or absence through some mechanical breakdown gives rise to disease. For example: insulin *versus* diabetes; liver extract *versus* anæmia; cortisone *versus* adrenal deficiency and a whole lot else; and, as we have already discussed, thyroid extract and thyroxine *versus* thyroid abnormality.

This broadening and deepening outlook on therapeutics is clearly reflected in the changing composition of official and non-official pharmacopœias. The old, and to us perhaps rather crude, materia medica – predominantly inorganic in kind and content – is giving place to a vocabulary of finer pharmacological texture – largely organic.

Not unnaturally, iodine has shared in this progressive movement, and Table I (*see* insert) shows how the British Pharmacopœia of modern days has taken on an entirely new look so far as iodine is concerned. Since 1864, there have been nine 'B.P.s' plus an addendum in 1960. Horizontal lines in colour mark the stages at which various iodine preparations were introduced, and the length of their survival as accepted therapeutic agents.

If one separates the inorganic monographs from the organic, that is, the simple from the complex, the upper and lower halves of the table – and take, for example, the 3rd 'B.P.' (1885) – one finds in it 13 inorganic iodine preparations and only one organic item, iodoform. Seventy-five years later (1960) only 6 basic inorganic, and 12 organic items are seen – an almost complete reversal.

On top, in red, are the parent substance, the strong and the weak tinctures, and potassium iodide – all with a record of one hundred years. Lugol's solution (5th on the list, top half) had a first innings of twenty years, was removed for thirty years, but was reinstated in 1948, and is still 'not out'.

Below, the organic members of the team are all comparative newcomers, and, as we have noted, are used for therapeutic purposes wholly different from those customary in former times. The switch in usage has been from skin disease,

venereal disease, and general tonic purposes (top half) to contrast media, thyroid therapy and the control of specific tropical diseases by organics such as chiniofon and iodo-hydroxyquinoline (lower half).

So much for the pharmacy and medicine of iodine.

Sources and Consumption

To occupy the time left at my disposal I would like to make a very brief historical note on the commercial sources of iodine, and upon world consumption as it was in the beginning and as it is today.

Table II (*see* insert) shows the average annual world consumption of iodine, decade by decade, for one hundred and twenty years from 1840 to 1960; and the amounts contributed to this consumption by the three great producing sources – seaweed (in green), Chilean *caliche* (in red) and underground waters (in blue). The totals are in metric tons; no data exist prior to 1840.

Seaweed, in which iodine was discovered, remained the only commercial source until Chile entered the field in 1868. Chilean iodine is obtained as a by-product during the elaboration of Chilean nitrate of soda from the raw material called *caliche* which occurs in vast natural deposits in Northern Chile.

From 1868 onwards, the Chilean share of the world iodine market gradually matured and overtook the seaweed share around 1880/1890. As a consequence, the seaweed contribution to world needs – provided mainly by France, Scotland and Japan, and with a zenith of 200 tons per annum in the decade 1910/1919 – gradually declined and fell to zero at the end of the Second World War. No seaweed iodine is produced to-day anywhere in the world, unless it be in Russia, which is doubtful.

In 1892 a new and powerful impact struck iodine commerce when workable quantities of the element were found in certain underground waters – mineral springs and natural brines, particularly in oil-field areas.

Java (in 1892) was the parent of this enterprise; California followed in 1926; Italy in 1927; and Japan in 1933. With the final elimination of all seaweed production in 1945, world needs are now supplied entirely from Chilean *caliche* and from underground waters in Japan, the United States, and Italy. To-day, world consumption lies between 2,000 and 2,500 tons – four times more than at the beginning of this century and twenty times more than one hundred years ago.

The figure mentioned excludes Russia and covers all fields of usage. Broadly speaking, 50% of the total is used for medical purposes; 30% goes into technical industry; and the remaining 20% into veterinary medicine and agriculture. This means that 1,000 to 1,200 tons are absorbed every year into pharmaceutical and medical use; and of this quantity 60% is converted and used in the form of potassium iodide.

These figures are near approximations. It is exceedingly difficult to obtain reliable statistics on the end-usage of iodine at any given moment of time. All sorts of unexpected factors and circumstances may intervene to upset one's calculations as, for example, when during the last war an exceptionally heavy and persistent demand arose in certain neutral countries for an iodine preparation called Entero-Vioform, sought ostensibly for the treatment of parasitic disease. In fact, this was none other than an attempt to smuggle iodine into Germany where supplies of crude material were non-existent. A more interesting irregularity occurred in the United States around the year 1927 when the iodine industry was surprised to notice an enormously increased demand for the alcoholic tincture of iodine. This was the era of prohibition in America, and it soon became apparent that the unprecedented sales of alcoholic iodine tincture were not for legitimate medical use, but simply to recover alcohol for 'bootlegging'.

Special legislation was introduced to control this nefarious trade, but not before 50 tons of iodine had been illegally diverted – representing approximately one and a quarter million litres of absolute alcohol.

What of the future? Who can tell how the reputations of iodine to-day will stand one hundred years hence? To venture an opinion, based, as it can only be, on the events of the past, I can only say that the process of research, revaluation, reappraisal, refinement, will go on, and that in the year 2061 some iodine merits that enjoy contemporary favour will plainly appear ephemeral, while new merits as yet hidden from us will assuredly have declared themselves. We may safely leave it to our successors to share the surprises that time has yet in store.

The 8-page insert accompanying this paper contains Tables I and II referred to in the text, a list of important dates in the medical history of iodine, and photographs of several of the great personalities who have helped to make the iodine story.

Meeting April 12 1961

Paper

The Use of Knowledge

by Austin Smith MD[1] (*Washington, U.S.A.*)

It seems only yesterday when the boundaries of knowledge were directly related to the geography of this world. As one moved from border to border of a country one thought of the knowledge contained therein and it was not difficult to compare nations with each other in terms of advancement and capabilities. This could be done in various fields: for example, medicine, economics, heavy industry, manpower and agriculture. In fact, from time to time warmongers tried to make plans to rule the world on the basis of such comparisons. Fortunately their judgment was as lacking as the advice they received; but they always left a trail of suffering and misery from which no nation emerged without some permanent damage.

This, however, was the misuse of knowledge. Inevitably, like misuse in any situation, it prepared the way for abuse. On the other hand, when knowledge is properly utilized, progress, benefits and happiness are possible for all. Since the wise use of knowledge depends in part on the avoidance of improper use it might have been better to entitle this paper 'The Use and Misuse of Knowledge', but time and a disposition to minimize the risk of abuse turned the pen to a more limited path.

A man to whom the United States will be forever grateful once wrote: 'I do the very best I know how, the very best I can, and I intend to keep doing so until the end. If the end reveals me as right, what is said against me will not amount to anything. If the end reveals me as wrong, ten angels swearing I was right would not make any difference.'

And so it is with the recording and application of knowledge. To emphasize this point and to prepare the stage for subsequent remarks, may I be permitted to summarize what might be called case histories? Each, and there are only two, pertains to situations in the United States. I ask your forgiveness for this display of provincialism but it seems more proper to speak about something within the country in which one resides than about a situation in another country. Furthermore, what exists in the United States is no different from what may be instanced in several other countries, including Canada where I was born and where I lived for a quarter of a century.

[1]President of the Pharmaceutical Manufacturers Association in the U.S.A.

The members of this audience are interested in health. And they are interested in accuracy. Without accuracy in observation, reporting and utilization, science moves slowly. Furthermore, there must be leadership in determining what is accurate and what is inaccurate. And finally, there must be a climate of freedom to encourage progress even in the health field.

Case History Number One

Earl W Kintner, formerly chairman of the Federal Trade Commission, a regulatory agency of the U.S. Government, recently declared: 'Both our political system and our economic system are grounded in the belief that the best society is the one which allows the individual the greatest opportunity for unfettered self-government. That belief in turn is grounded upon another article of faith, a faith that the individual in pursuing his self-development will demonstrate a decent respect for the needs of others, and a willingness to forego unlimited self-gratification at the expense of others. There is a deep realization that the exercise of the privilege of freedom entails the assumption of responsibility to others.'

In the history of your country and mine, freedom has been threatened many times. Our countries, like others, have known the meaning of war too often; and perhaps may yet learn even more. But freedom can be lost in other ways. In fact, some countries have lost certain freedoms without a drop of blood being shed. Freedom in research, in teaching, in medical journalism and in healing the sick are kinds of freedom over which physical wars are seldom if ever fought, and yet they can be the means through which a country may assume the cloak of the leader rather than the yoke of the follower.

Students of history will never forget Pearl Harbor Day, December 7, 1941. Eighteen years later to a day, the pharmaceutical industry in the United States had its own Pearl Harbor Day. And as was true for 1941 more people than those under direct attack became involved. On December 7, 1959, the pharmaceutical industry was con-

fronted with the opening of an investigation that swept far afield and had repercussions on many who were not involved in the making of drugs. The detailed conduct of this enquiry need not concern us. It is the results and consequences of the investigation that are important.

The fact emerged that the pharmaceutical industry in the United States had no corporate voice with which to defend itself against criticism and to remove misleading impressions. It became clear that the industry knew little about itself as a whole; it never had undertaken a large-scale public relations programme; and its discussions with government bodies in general had been at the regulatory level. Furthermore, the industry was not known to the public because it was not directly in touch with those who were sick but only with those who in one way or another treated the sick.

What, then, was to be done? The industry reacted both on an individual firm basis and through its national association. It made and initiated plans to gather and disseminate facts about itself and about those it serves. Members of the industry knew there were facts to give to the public, to the health professions, legislators, the press and others. And the industry hoped that as it became known as a source of accurate information, as well as of reliable drugs, it would find the public at large using the facts. This was not a time for confusion but for understanding.

Obviously the assignment was not easy. Earlier approach to the public had consisted merely of casual reference in the business columns of the press, in articles by science writers, or through some other equally impersonal channel. Few thought of the pharmaceutical industry as an industry, its members as entities, or even of its products as something worth while. Preoccupation was primarily with disease or symptom. In fact, so far as the general public was concerned, drugs and doctors were united as one, not drugs and drug manufacturers.

There were, then, four objectives for the pharmaceutical industry to achieve: (1) The gathering of information about the industry itself; (2) the dissemination of this information to interested groups; (3) the dispelling of confusion based on misunderstanding and lack of information; and (4) the exposure of trickery, deception and untruths where such existed.

This was when the use of knowledge assumed paramount importance. What was in the literature was a matter of record. Was it correct or in error? What often was needed was not available. Could it be obtained?

Mention is made of the situation solely because I asked for the privilege of telling two case histories. Each involves knowledge. The one relating to the drug industry reveals how important knowledge becomes when the lack of it can lead to misunderstanding, confusion and even harmful consequences. Needless to say, as the true facts were uncovered they were disseminated through many channels; but whether listeners and readers always related them to the accusations is an open question. Here is where those who work with the literature and with facts have a special challenge – yes, even an obligation – to make certain that history is interwoven with facts rather than bits of fiction.

Case History Number Two

Repeatedly over the past decade there has been criticism of the cost of medical care. Many questions have been raised in this area and many answers given – some of them conflicting. Too often, so it seemed, the answers were based on lack of facts. For example, many have said that drug costs are rising; medical care costs are getting out of hand; it is cheaper to die than to be treated medically. Such statements are made, of course, without true knowledge of the facts and without an awareness of the significance of the facts. To emphasize this statement permit me to be specific and again to refer to just one country, the U.S.A., since I am more familiar with it.

Drugs are said to be increasingly expensive. This is true if you compare the price of a new drug, which is curative, with an older drug, which at best was palliative. The new drugs do cost more but they offer more for the sick person. Furthermore, most prescriptions in the U.S.A. do not cost more than $3, slightly more than £1. In terms of *per capita* income, this is a small sum to pay for health and the ability to return to work. In addition, less of the medical care dollar is spent to-day for drugs than was the case even thirty years ago. And finally, the total medical care expenditures in 1959 represented only 6% of the total money spent by the public for personal needs. This, incidentally, should not be confused with total income since the latter was greater than the money spent for personal needs.

Perhaps such findings are more meaningful when reduced to other interpretations or related to facts less foreign to the average person in the street. For example, while the average prescription in the U.S.A. costs less than $3, the average

burial costs $900. This would seem to suggest it is not cheaper to die, at least in most instances.

Deaths from tuberculosis are only one-tenth of what they were fifty years ago. Deaths from pneumonia and influenza are one-sixth. Deaths from childbearing are about one-twentieth. And mortality among white males age 1 to 4 years has been reduced by 90%.

Another way of looking at the true cost of medical care is to think in terms of what some illnesses cost and what can be saved as these illnesses are brought under control. Mental illness costs the U.S.A. at least two and one half billion dollars per annum (say, £800,000,000). More than one-half of this is spent for maintaining patients in State, Federal and private hospitals. The rest represents loss of earnings and public assistance. But advances are being made rapidly in this field. Surgery, psychiatry and other specialties are contributing much to the solution all are seeking. Even drugs have made their contribution. So far, a drug cure for mental disorders has not been reported for general use but the tranquillizing drugs have offered more help than is generally appreciated. For example, in New York State Mental Hospitals, drugs reversed the upward trend for hospital needs and permitted the taxpayers to save millions of dollars while thousands of patients returned to useful lives.

Thus ends Case History Number Two, which is merely intended to dramatize the need for seeking and utilizing facts that are or can be made available.

Knowledge is the world's most important tool for constructing the foundation for advancement. In fact, it probably is about the only natural resource not yet even partially explored. And how tragic is any delay in the cultivation or application of knowledge particularly in the health field. This is illustrated effectively in a recent report issued by the U.S. Public Health Service. The report is entitled 'The Costly Time Lag' (1961, Washington) and refers to the time lag between the discovery and the application of medical knowledge. Briefly, the following points are made:

Even though millions of dollars are invested in the U.S.A. each year in medical research, unnecessary deaths and handicaps continue to occur because the knowledge gained from research is not fully used.

For example, in spite of methods for the early detection of cancer, this disease continues to cost each year 350 million dollars in hospital bills and more than 90 million dollars in lost income of workers. Loss in goods and services resulting from death in the age group 18 to 65 years has been estimated to be about 15 billion dollars (£5,000 million).

Glaucoma can be detected easily and painlessly, and 80% of it can be corrected. And yet it contributes heavily to the 90 million tax dollars spent each year for public assistance of more than 100,000 blind people.

Tuberculosis costs about 725 million dollars each year, most of this being met from tax funds. More than half is used for hospitalization.

In Minnesota a study was made of 1,000 persons who were hospitalized because of recurrent attacks of rheumatic fever. Their hospital and medical expenses amounted to 175,000 dollars. If they had been placed on a schedule of antibiotics to prevent a second attack probably 90% would have recovered. In fact, an examination of college freshmen who had a history of rheumatic fever revealed that less than 10% of those in need of continued treatment were receiving it.

Finally, a study made in one county in New Jersey of 177 severely disabled old people revealed that by putting them on a carefully designed medical-restorative service regime all of these patients learned how to take care of their personal needs. This reduced the monthly cost of medical care per patient from $300 to $104, a saving of $196 per patient per month.

What should be done about the medical knowledge that is available? Obviously it should be gathered, sorted, made intelligible and utilized. But how? And by whom? This is where everyone can play a part. The most difficult problem to-day seems to be not the financial underwriting of research but the accumulation of data and the general application of research findings. It is exceedingly difficult to decide what should be recorded in the literature, and then to find it after the entry is made. Librarians, better than any other group, know how knowledge can become useless as it lies buried in the literature. Researchers, too, know how difficult it is to separate the true from the false, the useless from the useful. And editors certainly are familiar with the formidable challenge inherent in the choosing of that which should be published from that for which there is no space.

Modern methods of storing, recalling and transmitting information will in time solve the problems of limited space. Microfilming equipment,

television principles and electronic gadgetry are providing aids almost impossible to appreciate let alone understand. Such modern methods will greatly assist those doing research and even those in conference. But how to identify and recover the knowledge being passed into the literature, and how properly to make use of it after it is recalled, are problems for solution not by machines but by humans. A machine will never replace the judgment of a properly qualified human mind in these respects, although it will of course reduce the drudgery of search and computation in the same way that machines are now being used by clinicians to aid the diagnosis of disease. In spite of the wizardry of modern machines, the attending physician will still have to depend to some extent on the laying on of hands, the use of eye and ear and the sense of smell and touch.

So it must be also with the use of knowledge. Machines will store and reproduce, but only the human mind can select what to store and how to use that which is recalled. There can be no substitute for reasoning.

It seems to me, then, that the use of knowledge is inseparably intertwined with human judgment, and that nothing has yet been found that offers even remote promise as a substitute for the latter. No matter how I view it I doubt if the human body and its brain will ever be replaced completely by a machine. Nevertheless, I am convinced that a wiser use of knowledge will be possible in the years to come if we study carefully how to use existing knowledge as it accumulates. Money, manpower, experiments, all of these and other things too,will be necessary to derive the most from that which we gather. But perhaps the single most important challenge will be the proper recognition of knowledge in our modern society. It is not based on formulæ and experimental animals, or storage cabinets and flight into space. No, it is based on human judgment, on the utilization of all contributing talents whether they be possessed by scientists, academicians, journalists or the press, and on the proper understanding of what and how each member of society can contribute. And in this respect I cannot think of groups that can make more substantial contributions than those identified with the development of medical knowledge. Without such knowledge all other achievements will have limited application. There would seem to be, then, a bright horizon for the men and women who work in this area and certainly the horizon should be especially bright for the members and supporters of bodies such as the Royal Society of Medicine.

Section of Epidemiology and Preventive Medicine

President J A Fraser Roberts MD

Meeting April 21 1961

President's Address

Human Genetics and the Public Health

by J A Fraser Roberts MD DSC FRCP (*London*)

There are a number of aspects of genetics which affect the health of the community. For example, there are the genetics of man's domesticated animals and plants. There are the genetics of the parasites which cause disease, as well as the genetics of the vectors of disease. Finally, there is the genetics of man himself. It is this last aspect only that I propose to consider in this Address.

With increasing knowledge, and with improvement in the conditions of life, early mortality has been greatly reduced. But the reductions under various headings have not been equal. Certain diseases and abnormalities do not share in this amelioration and so assume an ever-growing relative importance. These include conditions which are genetic or partly genetic. The figures for infant mortality for England and Wales during this century provide a striking example. They have been analysed by Martin (1949) for the period 1901–47, and data for subsequent years can now be added. Martin groups the causes of death under 13 headings. Under 11 of these the fall has varied from something substantial to something that can only be called phenomenal. One, namely injury at birth, shows an increase, but this is a subject outside the scope of this paper. Deaths attributed to congenital malformation have been practically stationary, and there has certainly been no fall. To the nearest whole number the rate has fluctuated in successive quinquennia from 4 to 6 per 1,000 births, the average figure being a little less than 5. There has been no general trend. Hence, whereas in 1901–05 one infant death in 32 was attributed to congenital malformation, the proportion is now about 1 in 5 or rather more.

Congenital malformations are sometimes, though not very often, wholly genetic. They are much more often partly genetic. But in many instances their cause is unknown, with little or no indication of genetic determination. A comparison which comes nearer to an assessment of genetic causation has been made by Carter (1956) who classified causes of death in children coming to post-mortem at The Hospital for Sick Children, Great Ormond Street. Table 1 shows a comparison of the years 1914 and 1954.

Table 1
Causes of death at The Hospital for Sick Children, Great Ormond Street

	Percentages			
Year	*Environmental*	*Unknown*	*Partly genetic*	*Wholly genetic*
1914	68	15½	14½	2
1954	14½	48	25½	12

Thus in 1914 environmentally determined conditions accounted for two-thirds of all deaths, the main causes being tuberculosis, intestinal infections and pneumonias. By 1954 the proportion had fallen to one-seventh. In Table 1 the conditions classified as of unknown origin include certain congenital malformations and the cancers of childhood. The partly genetic group includes such conditions as harelip and cleft palate, congenital pyloric stenosis and spina bifida.

It is more difficult to make comparisons in terms of morbidity; one particularly notable example, however, has been provided by Sorsby (1950). A survey of the causes of blindness amongst school children had been made by the Board of Education in 1922. Sorsby carried out a similar survey a quarter of a century later. The total rate had been halved during the interval, but blindness attributed to congenital and hereditary anomalies (including myopia) showed no reduction. Hence, whereas in 1922 37% of blindness in the school population was attributed to these causes, by 1950 the figure had risen to 68%. Sorsby emphasizes a finding which is probably true in a number of other fields as well. Over all ages, the relative importance of hereditary and congeni-

tal disorders as causes of blindness is much more marked in terms of total years of blindness than it is in terms of case incidence.

It is unnecessary to multiply examples further. It can be taken as a general rule that as mortality and morbidity fall the relative importance of hereditary and partly hereditary anomalies (as well as many whose causation is at present unknown) increases in greater or lesser measure, and often in very great measure. To some extent advances in therapy produce an absolute as distinct from a relative increase. Cæsarean section enables an achondroplastic dwarf woman to bear a living child, and half of these children will be similarly affected. Before the development of adequate treatment nearly all infants with well-marked congenital pyloric stenosis died; now they survive, and a proportion of their children are also affected. The repair of harelip increases the chance of survival and, later, of reproduction. Many treatable orthopædic conditions fall into the same category. These are specific effects, however, and it should be emphasized that there is no justification for generalizing them. There is no evidence, for example, that the decline in infant mortality generally (largely due to the conquest of infection) is preserving weaklings. The infants who previously died of scarlet fever, tuberculosis, gastro-enteritis or bronchopneumonia, would, in all probability, had they survived, have been as fit on the average as anyone else. Susceptibility and resistance (sometimes at least partly genetic) appear to be highly specific. There are no generalized qualities of 'weakness' or of 'strength'.

There is also the increased longevity of some of those suffering from congenital and hereditary abnormalities. For example, the proportion of mongols who now live on into adolescence and adult life has materially increased in recent years (Carter 1958). The extra burden to be borne by the family and the community in this as in other instances must be accepted, but it does again emphasize the increasing importance of the contribution of this category of anomalies to morbidity in our community.

Of course in those communities where mortality and morbidity are still very high a close interest in human genetics must appear somewhat esoteric. There are many immediate practical problems to be solved, with the hope of striking improvements within a relatively short time. But in communities like our own the scope for easy conquest has been greatly reduced and the more formidable long-term problems of inborn weaknesses and susceptibilities assume an evergrowing relative importance.

The transmission of genetic information from one generation to the next depends on the chromosomes and the genes they bear. The 46 chromosomes of the human cell nucleus, the 23 pairs, are very similar in principle to the magnetic tapes which actuate an electronic computer, providing sets of instructions which operate during development. The chromosomes are replicated at cell division with extraordinary precision. But, like all biological mechanisms, the replication can go wrong. Sometimes an entire tape, a chromosome, may be duplicated, or lost. Other major changes occur. Very often the change is confined to a single unit, that is, a single gene. All these changes may appropriately be called mutations. Mutation is going on all the time under natural conditions, each kind of change occurring with its appropriate frequency, which is very low. That is why the great majority of simply inherited defects are rare or very rare. There are very many of them, however, so in the aggregate their practical importance is far from negligible.

Some mutations are so unconditionally harmful that their possessors fail to develop or fail to reproduce. So these mutations get no further and have to arise *de novo* every time. Other mutant genes lower reproductive fitness. Then we get an equilibrium; the rate at which new mutations are fed into the population is balanced by elimination owing to the lowered reproductive fitness of their possessors. This is very immediately true of dominant genes, those which produce their effect when present on only one chromosome of the pair concerned. It is also true of sex-linked genes. With recessive genes, however, equilibria are easily upset and are not re-established for long periods. With harmful recessive genes, in fact, things are somewhat different. If the gene is truly recessive, that is, only produces its effect when present on both members of the chromosome pair concerned, natural selection only operates on those individuals who happen to carry the gene in double dose. Such individuals are rare compared with people who carry the gene in single dose only, that is, the heterozygotes, as is shown in Table 2.

Table 2
Relative frequencies of heterozygotes and homozygotes

Frequency of gene	*Frequency of heterozygotes*	*Frequency of homozygotes*	*No. of heterozygotes for each homozygote*
1 in 20	1 in 10·5	1 in 400	38
1 in 50	1 in 25	1 in 2,500	100
1 in 100	1 in 50	1 in 10,000	200
1 in 500	1 in 250	1 in 25,000	1,000
1 in 1,000	1 in 500	1 in 1,000,000	2,000
p	2p (1–p)	p^2	$2p(1-p)/p^2$

Harmful recessive genes, then, are common; what is uncommon is the chance of their coming together in pairs.

Occasionally harmful genes and their manifestations are not rare. The gene which in single dose produces the sickle-cell trait, and which produces sickle-cell anæmia when in double dose, is very common in Africa north of the Zambesi. It reaches a frequency of as much as 25% in some places, which means that some 40% of the population carry the gene and some 6 or 7% of children suffer from sickle-cell anæmia. The gene which in double dose gives thalassæmia major, Cooley's anæmia, is very common in parts of the Mediterranean basin, reaching a maximum frequency of about 10% in certain townships in the district of Ferrara in Italy. This corresponds to one carrier in 5 and one case of Cooley's anæmia in every 100 births. There has to be a reason why such harmful genes have become so common in some areas. This is the existence of balanced polymorphism; there must be a corresponding advantage.With the sickle-cell gene the advantage is at least partially due to the greater resistance of the carriers to malignant tertian malaria. This advantage of the more numerous carriers balances the loss of nearly all the homozygotes. There must have been a similar advantage attaching to the carriers of the thalassæmia gene; it also may have been greater resistance to malaria. We can in fact be sure that if an apparently harmful gene reaches an appreciable frequency there is, or has been, a balance of advantage and disadvantage. The commonest harmful single gene in our country is that causing fibrocystic disease of the pancreas, with a frequency of perhaps as much as one in 1,600 births. Here, too, there must have been a counterbalancing advantage somewhere.

The great bulk of hereditary variation, however, is multifactorial. Many genes of individually small effect combine in an additive way to give the final result. This is the kind of variation which underlies most of the differences between normal human beings. This kind of variation is important in relation to disease, for it probably provides the hereditary component in differences between individuals in susceptibility and resistance.

Then there are the partly inherited conditions. Sometimes the genetic basis may be single genes, or it may be multifactorial. In fact, with the rarest of exceptions, environmental influences can be seen to contribute appreciably or substantially to the variation of traits whose genetics is multifactorial.

Now what can be said about applications of genetic knowledge and the health of the community? Let us start with the most fundamental considerations, though these are not necessarily of most immediate practical importance. First of all we do not want to raise mutation rates artificially more than is strictly necessary; for in the nature of things the great bulk of mutations are harmful; the occasional beneficial mutation must be rare indeed. Mutation rates are greatly speeded up by ionizing radiation and also by some other agencies, including certain chemical substances. But it is ionizing radiation which is of most immediate importance. There are the industrial uses of X-rays and radioactive isotopes, for example. By far the biggest contribution in our population at present is due, however, to the diagnostic use of X-rays. The danger should not be exaggerated. The total exposure of the population is still relatively low compared with background radiation, and the amount of induced mutation must be small compared with that occurring naturally. Nevertheless, there is no reason to believe there is a threshold. Any exposure, however small, makes its due contribution, even if we now know that the induction of mutation increases disproportionately at higher dosages. But we want to keep the feeding of mutant genes into the population to as low a level as possible. Care in the use of industrial radiation, the avoidance of unnecessary X-rays, the shielding of the gonads and the development of apparatus with low energy requirements will all make their due contribution. It should be added here, for completeness, that even fairly large increases in mutation rates would have a relatively small effect on characters determined by multifactorial inheritance.

The possible importance of the direct and immediate effects of mutation has been emphasized during the last two years with the discovery that major chromosome rearrangements are not at all uncommon. Mongolism is due to the presence of an extra third chromosome belonging to one of the small pairs. With the rarest of exceptions mongols do not reproduce and the rather different mechanism whereby the extra chromosome 21 is attached to another chromosome and so can be transmitted by outwardly normal carriers is of rare occurrence compared to the usual picture of an extra chromosome whose presence is directly due to a mutation, so that the condition arises *de novo* in the great majority of instances. Mongolism has a frequency of about one in 500 births, so it is far commoner, in our population at least, than any defect due to a harmful single gene. The same thing is true of Klinefelter's syndrome, small testes and infertility associated with rather slight alterations in male sexual development. It is due to the presence of two X chromosomes and a Y instead of the one X and one Y of the male, or the two X's of the female. It has a frequency of the order of no less than one in every

300 to 500 births. There are other abnormalities associated with major chromosome aberrations, including the triple-X woman, who is probably not especially rare and in this instance often fertile. It is likely that ionizing radiation increases the frequency of non-disjunction and the other less common processes by which these major mutations arise.

Most of the major aberrations are not transmitted to future generations, so any increase or decrease is an immediate one. It is quite different with single mutant genes. Here the load is being largely built up at the expense of future generations.

There is a second way in which the frequency of major mutations, and perhaps other mutations, may be influenced. This is the effect of rising parental age. As is well known in mongolism, the incidence amongst the children of young mothers is low, not more perhaps than one in 3,000 births. With advancing maternal age the incidence rises at an increasing rate, so that amongst the offspring of the oldest mothers of all the figure rises to something of the order of 3% (Böök *et al.* 1958). It is probably true that Klinefelter's syndrome also occurs more frequently as parental age rises and it would not be surprising if it were generally true in greater or lesser degree of most or perhaps all major mutations, though it seems unlikely that rises will be found to be so steep as with mongolism. Furthermore, it may be that advancing paternal age, that of fathers as well as mothers, may have a relation to an increased frequency of single gene mutations. Here, then, is a very practical and, theoretically at least, controllable factor in the damage directly done by mutation and also done by the feeding into the population of harmful genes which will duly affect the welfare of future generations. Having children early could produce a very appreciable direct effect and probably also some long-term effect.

So much then for the extra flow of new mutant genes into the population. We must next consider what can be done with the genes we already have, and are bound to have. Some reduction in the number of harmful genes can be expected if their possessors limit their families. To some extent this happens already. There is a tendency for family limitation amongst those who have children suffering from serious developmental defects. I am not suggesting for a moment that there should be any dictation to parents as to the number of children they should have, and not even that they should be advised not to have children. But undoubtedly with growing knowledge, and an awareness of risks not previously appreciated, increasing numbers of people will do so voluntarily when there is a big risk that children or further children may suffer from some serious abnormality. This raises the question of genetic advice to patients, a subject I should like to deal with in a little more detail.

The proportion of the population who really need genetic advice in regard to marriage and children is relatively small, but those who do need it need it badly. Sometimes the question arises before marriage; one or other partner may suffer from a condition which may be transmitted to children, or there may be something in the family history which, it is feared, may imply an extra risk to offspring. More often advice can only be sought after the event, for it is only the birth of an affected child that reveals the potential risk. Then the question is whether or not there is a chance of recurrence in a subsequent child.

Naturally, the choice is that of the individual couple, but there is some automatic contribution to the health of the community by the limitation of families where there is risk of abnormality; some harmful genes are thereby reduced in frequency; others are prevented from coming together in harmful combination. Important though this negative aspect may be, and it is important when the risks are high, it is probable that another consideration is of equal or even greater importance. The welfare of the unborn child is the subject of a rich store of ancient and widespread beliefs. Old wives' tales are usually gloomy, so very often couples think that the risk is far greater than it really is, and refrain from parenthood quite unnecessarily. Even when medical advice is sought the risks may be overestimated, and it is probable that the harm done in this way is greater than the consequences of taking too favourable a view.

The provision of genetic advice for those who need it, which I would suggest should be a part of any health service, involves more, however, than the calculation of chances for offspring or further offspring. Deep emotions are involved; the decision may well be for life. Often there are overt or unconscious feelings of guilt. There may be a sense of loneliness, of being unlike other people. Wise advice from the family doctor and at the health clinic, in addition to specialist genetic advice if this is needed, can help to reconcile patients to their misfortune or deprivation. A very important point is reassurance, when this can properly be given, about the chances in regard to marriage and offspring of normal children and other normal relatives.

It is very necessary that the medical adviser

should appreciate fully the considerable risks involved in any random pregnancy, the risk that the child will suffer from some serious congenital or hereditary abnormality, or that some serious developmental defect will manifest itself during early life. A figure of 1 in 40 is probably not too high. Apart from helping to assess the seriousness of any special risk discussion along these lines helps patients to realize that they are not different from other people. All prospective parents are inevitably running risks, though only a proportion are unlucky.

Dominant genes,[1] directly and visibly transmitted from parent to child, raise few problems. Many tend to be relatively innocuous, and I cannot see why those with polydactyly, or syndactyly, or congenital cataract, should not have children if they want to. There is, however, one very important exception, namely Huntington's chorea. Owing to late manifestation the majority of sufferers have had the opportunity of producing a family before the disease becomes apparent. The admirable surveys of Pleydell (1954) in Northamptonshire showed how valuable it would be to make a complete ascertainment and inform potential sufferers of the risks to children that are involved. Many in these families told Pleydell that they would never have married and had children had they known the facts.

Sex-linked genes pose rather more difficult questions, and often produce results of greater severity. The commonest in our population are hæmophilia, or rather the hæmophilias, and muscular dystrophy of the classical Duchenne type. Here the difficult choice is for sisters of affected boys. Any such sister has one chance in two of being a carrier and so there is one chance in four that any boy will be affected or any girl in turn a carrier. All the daughters of a hæmophilic man will be carriers. It should be added that the risk for a sister is lowered, though not very appreciably, if her affected brother is the first to be affected in the family group, and so possibly a mutant.

Half the sisters of affected boys are on the average carriers, and it would be of the greatest value to know which. The lucky ones could be reassured, and of course the high risk confirmed for the others. With some sex-linked conditions the carriers can be distinguished by lesser symptomless manifestations. This is true, for example, of the rather rare sex-linked form of retinitis pigmentosa and of choroideræmia. Unfortunately it is not yet so with the two most important conditions, muscular dystrophy and hæmophilia; but it may be hoped that the detection of carriers of those conditions may be achieved in the future – and a notable advance it would be.

Many abnormal conditions, including some of considerable numerical importance, like the major malformations of the central nervous system, harelip and congenital pyloric stenosis, appear to be partly genetic. When a couple have had a child with spina bifida the risk of recurrence in a subsequent child is about 1 in 25. When a couple have had 2, the risk is increased to something like 1 in 7. Whether refraining from having further children would have any appreciable effect in reducing the harmful genetic load in the population is distinctly doubtful; but, as always, there is the direct contribution of some reduction in the numbers of affected persons actually appearing.

With recessive genes the main problem is quite different; it is how to prevent the harmful genes coming together in pairs. When in single dose they do little or no harm; sometimes they may be actually beneficial. One way depends on being able to recognize the heterozygotes, who can then be warned of the danger of marrying each other. This is already being done on a large scale in Italy in connexion with the thalassæmia gene. Facilities for registration are provided so that prospective marriage partners can be warned, if both should chance to be carriers, of the risk of 1 in 4 that any child may suffer from Cooley's anæmia. Of course, it is a little late to discover the risk when the banns have been read and the wedding invitations sent out; but one imagines that the knowledge that two people are carriers might well prevent those earlier approaches that ultimately lead to courtship and marriage. Doubtless, before long, similar facilities will become available in Africa for the routine detection of carriers of the sickle-cell gene, with the ultimate promise of a great reduction in sickle-cell anæmia.

It may be that in our own country, provided efficient tests become available for recognizing the carriers, it may become worth while to provide facilities for the detection of carriers of some of the rather more common recessive genes, for example fibrocystic disease of the pancreas, where something like 5% of the population can be assumed to be heterozygous.

It may fairly be asked at this point, is a policy of preventing harmful genes coming together in pairs an interference with the processes of natural selection, which removes two genes every time they do so? Are we not contributing to the in-

[1]The argument of this and the next half dozen paragraphs has been somewhat expanded elsewhere (Roberts 1961).

crease of the harmful genes in the population? The answer is that the effect is so small that it cannot become appreciable for many generations, and by that time knowledge will doubtless have been transformed. Harmful recessive genes are common, probably in all species with sexual reproduction, and certainly in man. Estimates of the number of harmful recessive genes (or their equivalents) carried by the average human being range from 3 to 8. We all carry them; but most of us have the luck to marry someone not carrying our own particular brands, but some others instead. Moreover, owing to the small size of human families, often the 1 in 4 chance does not come up, so that there are very many couples in the population who do carry the same harmful or lethal gene, but have been lucky in having 1, 2, 3, or 4 normal children. They can never know the peril that was there all the time. It seems to me there is no reason at all why known carriers, or sufferers provided they can reproduce, should not have children if they want to. Those who have children with recessive defects are no different from anyone else except that they have been unlucky. The important point is that abstinence from further children once the defect has appeared, and the avoidance of the marriage of carriers, as this becomes practicable, is capable of reducing considerably the proportion of affected children.

There is another and a more general consideration governing the coming together of harmful recessive genes in pairs. This is the marriage of blood relatives. Given random mating the likelihood of identical genes coming together in the child is determined by the frequencies of those genes in the population. The chance is increased when blood relatives marry each other, for a proportion of their genes are necessarily identical, being derived from the same ancestor genes. The proportion necessarily the same is, for example, 1 in 8 for first cousins. The remainder of the genes may be the same or different, with probabilities which are the same as in the marriage of unrelated persons. Clearly the risk of rare recessive defects appearing is increased in consanguineous marriages, but what is important to the individual couple is not the increase in the relative risk, but the amount of the absolute risk. Looked at rather theoretically, almost the only way until fairly recently, the amount of the increased risk has not seemed very large, or of a size that would be a serious deterrent to sensible persons informed of the facts. But, of course, small risks to given individuals may represent serious risks to the community as a whole, and from every point of view the direct test of observing the results of consanguineous marriages is a most desirable goal.

In recent years some very informative studies have been carried out, including those of Sutter & Tabah (1952), Böök (1957), Schull (1958) and Slatis *et al.* (1958). The results show a very considerable measure of general agreement. There is little difference between the outcome of consanguineous and control marriages up to and including birth. That is, the interval to first conception is no longer; there are very few more miscarriages, and there is no excess of stillbirths, provided those due to recognizable major deformities are excluded. Thus the effect of increased homozygosity does not seem to operate by causing early wastage. From birth onwards, however, the findings are different. Thus Schull (1958) found a death-rate at Hiroshima (this has nothing to do with the atomic bomb) of 116 per 1,000 during the first 8 years of life amongst the offspring of first cousins, against 55 amongst the controls. The proportion of major congenital abnormalities was rather less than doubled. Slatis *et al.* (1958) studied a sample at Chicago. With a lower total death-rate the difference in this respect was naturally greater. Amongst the offspring of consanguineous unions the death-rate by the age of 10 years was 81 per 1,000 compared with 24 per 1,000 in the controls.

A very striking fact is that only a few of the deaths were due to recognized recessive conditions and the same is true of the congenital malformations not necessarily resulting in death. Multiple congenital defects figure prominently, and these have not hitherto shown any particular indication of being genetic. There are no obvious explanations at present. It may be that a rather small proportion of genetically determined cases have been lost amongst the remainder. Or it may be that recessive genes with a low frequency of expression are concerned. Or, perhaps, it may be that the effect is more general, that the tendency to homozygosity at a number of loci is unfavourable. It is clear, however, that the extra risks of consanguineous marriage, even if not very great for the individual couple, are quite considerable when taken in total from the point of view of the community. The problem is not an urgent one in communities like our own in which the rate of first-cousin marriages has fallen to a very low figure, not more perhaps than 3 per 1,000, and is still falling. In some countries, however, consanguineous marriages are still relatively frequent, for example 10 and even 15% for first-cousin marriages in parts of Japan. It is of advantage to the health of the community that these frequencies should diminish; an outbreeding human population is a healthier population, and this not only because of a falling off in definite, known, recessively determined defects.

We must now pass to the next stage. The gene is there; it has produced its effect. Of course a number of genetic or partly genetic defects are treatable, as for example with many orthopædic conditions, or with harelip. Often this is a matter of straightforward medicine or surgery. But sometimes early diagnosis is very important and this, I take it, is relevant to the field of preventive medicine. For example, galactosæmia is a metabolic anomaly due to a recessive gene. The body cannot utilize lactose. Diagnosis is not easy and early death is a common sequel. Moreover, even should the child survive, irreparable cerebral damage will often have taken place, resulting in mental deficiency. Early diagnosis and the use of milk substitutes can secure normal development. As the condition is recessive the chance of making an early diagnosis is often confined to a second or later child. But at least the subsequent children of parents who have had an affected child can be watched from birth. Nephrogenic diabetes insipidus provides another example, as shown by Carter & Simpkiss (1957). Early diagnosis is again difficult, early death is common, and should the child survive, the profound dehydration often results in mental deficiency. Prompt recognition and appropriate treatment, with ample fluids, should lead to relatively normal development. This condition is due to a sex-linked gene, and in this instance not only is a family history of the condition of value in making an early diagnosis, but there is the immense added advantage that the female carriers of the gene can always, or nearly always, be identified by their failure to produce a normally concentrated urine. Once these women are identified it is known that the chance that any son will be affected is 1 in 2.

Phenylketonuria is due to a recessive gene. The body is unable to utilize phenylalanine. Toxic products accumulate and the result is almost always cerebral damage so severe as to cause profound mental deficiency. It is now known that feeding on a diet almost free of phenylalanine may effect much improvement in the mental state, and perhaps in favourable instances the intelligence level may be kept within normal limits. But the treatment, to be effective, must be started early in life. In the ordinary way a sufficiently early diagnosis may only be made with a second affected child. The incidence of the condition in our population is no more than about 1 in 40,000, but the chemical test is so simple that there is a good case for carrying it out on all children soon after birth. Experiments on these lines are already in progress.

I now come to a final stage at which genetics may be relevant to prevention. With some genes there are special risks to which the bearers are exposed and from which they can be protected. Some of these hazards are natural; lactose in galactosæmia has already been mentioned, but the most important and interesting are new risks, of a kind that did not exist before, risks created by modern therapy, and especially drug therapy. A notable example is provided by a gene which in double dose determines a very low level of pseudocholinesterase (Lehmann & Ryan 1956). Under natural conditions the gene produces no harmful effects; at least none have been discovered so far. But if the homozygotes are given suxamethonium as a muscle relaxant during anæsthesia they are liable to develop an apnœa which may be fatal. It is a remarkably frequent gene, about one person in a thousand having it in double dose. It is most important to identify these people as far as possible and make sure that if they are undergoing operation they should not receive suxamethonium. Already in the course of family studies such susceptible persons have been identified and given cards explaining the risk.

Another gene, which is very common in negroes, was discovered during the course of antimalarial therapy. Hence the condition is often called primaquine sensitivity. This is a sex-linked gene, and amongst the negroes in the United States about 14% of men carry it and so are affected. The corresponding frequency of affected women is about 2% (Childs *et al.* 1958). Again there must be a reason why such a gene should have become so common in certain populations. On the basis of distributions in Africa associated resistance to malaria has been suggested (Motulsky & Campbell 1960). The metabolic anomaly is a deficiency of glucose 6-phosphate dehydrogenase. Again, under natural conditions, apart from trouble if favus beans are eaten, the gene seems to do little if any harm, but administration of primaquine, phenacetin, sulphanilamide, or several other drugs, produces a hæmolytic anæmia. Anæmia may also occur in those addicted to the curious habit of eating mothballs.

Yet another, and a very interesting example, comes from South Africa. In that country a form of porphyria due to a dominant gene is very common (Dean & Barnes 1955, Dean 1961, personal communication). It is estimated that there are no fewer than 8,000 affected persons, and all can be traced back to one couple, who married in 1688. In men the manifestations are mainly cutaneous, while in women the characteristic features are abdominal pains, vague symptoms often considered neurotic, and abdominal crises. Under natural conditions affected persons get on well enough, as is made abundantly plain by the astounding multiplication of the gene. But

certain drugs may prove disastrous. The most dangerous are barbiturates, and particularly thiopentone anæsthetics. The likelihood of women being given barbiturates because of supposed neurotic symptoms and, worse still, thiopentone in childbirth, or what is supposed to be an acute abdominal condition, is very great. Many deaths have been reported. Now the danger is recognized, thanks to the work of Dean & Barnes, and it has become routine at many hospitals in South Africa to test for porphyria prior to giving an anæsthetic, and also to provide those bearing the gene with cards explaining that the dangerous drugs must on no account be given.

It is likely that the list of drug-induced diseases will grow rapidly. In fact, the general question of genetically determined reactions to drugs is likely to provide an increasingly rewarding field for research. In passing I might mention the difference between slow and rapid inactivation of isoniazid, a difference which seems to be genetic. It may be that it is the slow inactivators who do well on this drug, which may have practical consequences in the treatment of tuberculosis.

As regards the general question of particular dangers threatening those genetically predisposed to certain common diseases which have some constitutional background I do not feel inclined to say more than a word. The strength of the genetic predisposition is often not very great and we do not yet know enough to make the application of genetic knowledge particularly useful in detection and control. But this may be changed in the future. In addition to special protection against rather special dangers, it may well become increasingly possible to recognize particular dangers to certain individuals in connexion with common diseases and so to take useful steps towards prevention.

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Joint Meeting June 23 1961 with the Medical Section of the Royal Statistical Society at the Road Research Laboratory, West Drayton, Middlesex

Road Accidents

The following papers were read:

Epidemiological Aspects of Motor Cycle Accidents
Dr P W Bothwell (*Bristol*)

Damage to Motor Cars and Injuries to Occupants
Dr J D Morland (*Road Research Laboratory*)

Enquiry among People Injured on the Roads
Dr R M Collister (*Road Research Laboratory*)

Section of Ophthalmology

President Sir Benjamin Rycroft OBE FRCS

Meeting January 12 1961

Papers

The Uses of Acrylic[1] Anterior Chamber Implants Illustrated by Cases Shown

by D P Choyce MB DOMS FRCS (*London and Southend*)

I am very grateful for this opportunity of showing and discussing some of my cases. I asked the Secretary of the Southend General Hospital to let me know the present total of implants used and paid for by the Southend-on-Sea Hospital Management Committee. He informs me that 308 implants have been used to treat 290 patients (302 eyes: *see* Table 1). In addition to the 12 bilateral cases there are 6 cases where I found it expedient to change one implant for another.

Table 1
Uses of Acrylic Anterior Chamber Implants (302 cases)

	Condition	No. of eyes
Wholly transparent implants	(1) Uniocular aphakia	251
	(2) Binocular aphakia (9 cases)	18
Optical	(3) Uniocular high myopia	5
	(4) Binocular high myopia (1 case)	2
Mechanical & Optical	(5) To assist with penetrating keratoplasty	5
	(6) To assist with treatment of aphakic retinal detachment	2
'Occlusive' implants	(1) Cosmetic use	2
	(2) Relief of diplopia	1
Implants with clear optic and coloured opaque haptic	(1) Traumatic iris coloboma plus aphakia	4
	(2) Traumatic iris coloboma in phakic eyes	2
	(3) Ocular albinism: both eyes of 2 patients	4
	1 eye of 5 patients	5
	(4) Traumatic mydriasis	1

[1]Acrylic is the family name for most plastics. It would be more correct to state that all the implants used by me are manufactured from cast polymethylmethacrylate or Perspex C O. 'Acrylic' is retained for the sake of brevity.

There is not time to discuss why I regard this implant (Fig 1) as the one of choice. I would refer those interested to my other papers on the subject (Choyce 1960*a*, 1961*b*, *c*).

Experience has shown that careful attention to a number of small points makes all the difference between consistent success and occasional success. These points are disregarded at the surgeon's peril. An example of anterior intraocular iris prolapse was shown to me by an American colleague in New York last June. I asked to see a pre-operative picture of the eye which revealed that no preliminary superior iridectomy had been performed. I have always stressed that if this step is omitted pupil block will occur during the immediate post-operative period, aqueous will accumulate behind the iris, pressing it forward so that the pupil margin is forced in front of the anterior chamber implant where it becomes trapped.

Illustrative Cases

Case 1 R P, male, aged 5
Bilateral congenital cataract, left more than right. Worse eye treated by linear extraction followed by anterior chamber implant
Operation was indicated by increasing amblyopia, divergence and elevation of the left eye which did not respond to right occlusion. At the age of 4 years surgical treatment was begun. Three operations were necessary to extract the cataract and to do an adequate superior iridectomy while leaving the posterior capsule intact. Four months after the first operation a thin haptic anterior chamber implant was inserted (fourteen months ago). With continued occlusion of the right eye the left vision came up to 6/12 with 0 D.S./−2·5 D. cyl. axis 180 degrees. The divergence remained stationary but was improved by recession of the lateral recti. The present position is that the vision is 6/9 right and left without glasses. The implant is lying vertically. Post-operative anterior chamber depth is 1·7 mm.

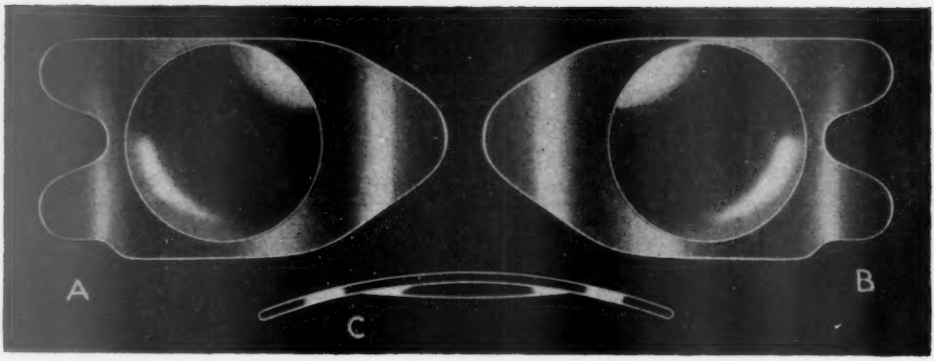

Fig 1 *Anterior chamber implants.* **A,** *for right eye, and* **B,** *for left eye; note inferior ledge.* **C,** *implant profile to show increased radius of curvature and 0·5 mm thick haptic portion*

Case 2 M H, male, aged 11
Left uniocular traumatic cataract under the age of 10
At the age of 6 the left cornea was perforated, followed by a traumatic cataract. This was successfully treated by Mr Edward Bacon of Southampton who then tried to fit this boy with a contact lens. It was not possible to establish satisfactory tolerance and by the time he was 9 years old the vision had dropped to 6/24 with correction through the onset of amblyopia. Mr Bacon referred the case to me with a view to insertion of an anterior chamber implant. A preliminary superior iridectomy was performed and a fortnight later a thin haptic anterior chamber implant was inserted. The right eye was totally occluded for two months, which brought the vision up to 6/9. There has been no further need for occlusion and the acuity has now improved to 6/5−2 with 0 D.S./−2·75 D. cyl. axis 7½ degrees. Full binocular single vision is present. This patient leads a normal life for a boy of his age except that he is not allowed to box or to play Rugby football. Post-operative anterior chamber depth is 2·1 mm.

Case 3 V B, female, aged 13 (from New Zealand)
Right uniocular traumatic cataract under the age of 10
In 1956 she sustained an almost vertical corneal incision in a car crash. Traumatic cataract developed, which was needled in 1957. The corrected vision at that time was 6/9. An unsuccessful attempt was made to fit her with a contact lens. The insertion of an anterior chamber implant was considered in New Zealand and it was decided to leave it for some years. By 1960 the corrected vision had declined to 6/24. No evidence of binocularity could be elicited. The parents decided, however, to have an anterior chamber implant inserted. The refraction was +11·5 D.S./−2·5 D. cyl. axis 155 degrees.

If an anterior chamber implant is introduced through the usual temporal incision from 7 to 11 o'clock on the right eye some 2·0 to 2·5 dioptres of myopic astigmatism result through the healing of the incision with the axis roughly horizontal. If the usual technique had been employed in Case 3 the resultant astigmatism would have been −4 to −5 D. cyl. axis approximately horizontal. Experience has shown, however, that it is possible to insert these implants either horizontally or diagonally up to an angle of 50 degrees with the horizontal. In Case 3, therefore, the preliminary iridectomy was sited between 10 and 11 o'clock and the incision was made from 5 to 9 o'clock instead of the usual 7 to 11 o'clock. The implant was inserted diagonally and now lies at 30 degrees with the horizontal. When the corneal incision has fully healed the resultant astigmatism should largely cancel out the pre-existing astigmatism instead of adding to it.

July 1961: V B is now back in New Zealand, under the care of a colleague who informs me that the visual acuity is 6/18 unaided, not significantly improved by glasses, and with no residual cylindrical error.

Case 4 Mrs H, aged 63
Left uniocular aphakia – cataract secondary to heterochromic cyclitis
Four years ago left extracapsular extraction was performed with peripheral iridectomy. March 1957, left capsulotomy. April 1957, left thick haptic anterior chamber implant inserted. January 1961, right vision 6/5, left 6/9 with 0 D.S./−4 D. cyl. axis 15 degrees.

In 20 of my cases of uniocular aphakia the cataract was secondary to heterochromic cyclitis. These cases form a most interesting series which prompt the following observations: (1) The eyes withstand implant surgery very well considering that they are the seat of a chronic cyclitis.
(2) The inflammatory deposits tend to settle on the front and back of the implant in preference to the back of the cornea.
(3) These cases have a tendency to develop secondary glaucoma which is in keeping with the natural

history of the disease. Case 4 has this tendency, but it is controlled by pilocarpine 2% drops b.d. and Diamox 125 mg b.d.

(4) In Case 4 muscle balance was normal, but she had only 30% stereoscopic vision.

(5) The anterior chamber depth is 2·0 mm, rather more than the average (1·68 mm) obtained with the thick haptic implants.

Case 5 Mr B, aged 44

Right long-standing traumatic aphakia with superadded divergence and depression

At the age of 13 he received an injury to the right eye resulting in uniocular cataract which was treated surgically at that time. Thirty years later he had marked divergence and depression of the right eye, the vision of which was, however, 6/12+ with correction. The usual preliminary iridectomy was carried out and a fortnight later a thin haptic anterior chamber implant with inferior ledge was inserted (eight months ago). The vision slowly improved as the reaction subsided and is now 6/9+ with a small correction. In recent months he has had a recession of the lateral recti, resection of the right medial rectus, and recession of the right superior rectus. He now has 6 prism dioptres of hypertropia and 6 prism dioptres of exophoria, and experiences a little diplopia but not enough to worry him seriously. Post-operative anterior chamber depth is 1·9 mm.

Case 6 A W P, male, aged 69

(1) *Right long-standing uniocular traumatic aphakia*

(2) *Left acute narrow-angle glaucoma*

The cataract was the result of being struck in the eye by a whip when aged 10. It is not known for certain how long the cataract took to develop. It was, however, mature by the time he was 64; it was extracted intracapsularly with a complete iridectomy. Two months later a thick haptic anterior chamber implant was inserted. His vision is 6/9+ unaided and he also has full binocular vision. There was thus an interval of fifty-four years between injury and the restoration of normal visual acuity and normal binocular function. *The implant was inserted five years ago* and the result continues to be satisfactory in spite of chronic coughing, the result of bronchitis and emphysema. Two months ago he was admitted as an emergency with acute angle-closure glaucoma in his other eye, which was treated surgically.

Case 7 J H, male, aged 89

Left uniocular senile cataract

This case demonstrated that advanced age is no barrier to the use of an anterior chamber implant.

For many years the patient had been dependent on the right eye which contained early stationary lens opacities with a vision of 6/9. The left lens became hypermature and intumescent; the anterior chamber was dangerously shallow and the history suggested prodromal attacks of acute narrow-angle glaucoma. Intracapsular extraction was therefore performed when he was 87. The visual result was 6/9 with correction but he experienced intolerable diplopia when trying to use the two eyes together. Although it had been explained to him before the operation that it would almost certainly not be possible to provide him with glasses, he was very disappointed that this was so.

The patient is now 89 and the anterior chamber implant operation has been successful. Post-operative visual acuity is 6/9 with −0·25 D.S./−2·0 D. cyl. axis 15 degrees. Binocular single vision is present. Post-operative anterior chamber depth is 2·2 mm.

The treatment of recent traumatic uniocular aphakia in children under the age of 10 has always been a difficult problem. Generally speaking the younger the child the denser the amblyopia and the more rapid its development. Theoretically, it is possible to get these children past the age at which amblyopia will occur by the provision of an aphakic correction plus occlusion of the undamaged eye. In practice, however, this line of treatment, which may have to be maintained for several years, imposes a severe strain on patients, parents and teachers and it is unusual for it to prevent the occurrence of some degree of amblyopia and loss of binocularity.

Under these circumstances, in the present state of our knowledge of anterior chamber implants as illustrated by some of the cases I have described, there is clearly much to be said for the introduction of a suitable anterior chamber implant as soon as possible after the cataract has been dealt with. If this is not done many of these patients will inevitably spend their adult life virtually as one-eyed persons because of dense and irreversible amblyopia of the injured eye.

Case 8 J S, male, aged 23

Bilateral congenital cataract needled in infancy, fitted with bilateral anterior chamber implants in later life

The patient went to the Blind School at Great Yarmouth and learnt Braille. By the age of 23, right and left vision was 6/60 with +11 D.S. In April 1960 a preliminary iridectomy was followed, a fortnight later, by insertion of an anterior chamber implant. Two weeks later similar treatment was carried out on the left eye. Right and left vision is now 6/36 and N 8 with a reading addition. The nystagmus is possibly less. The patient states that the principal improvement he notices is in an improved field of vision and better distance vision. He has much greater confidence when using public transport. He is no longer registered as blind nor as partially sighted. Anterior chamber depth is 1·9 mm right and left.

Case 9 Mrs F, aged 25

Right uniocular high myopia

Pre-operative refraction: Right vision 6/18 with −10 D.S./−1 D. cyl. axis 30 degrees; left vision 6/9 partly with −1·75 D.S./−2·0 D. cyl. axis 10 degrees.

She could not wear this correction because of diplopia and asthenopia. It was not possible to fit her with a right contact lens to overcome the anisometropia and the resultant aniseikonia. After the usual preliminary superior iridectomy, an anterior chamber implant was inserted, slightly diagonally from 10 to 4 o'clock. The present vision is right 6/12 unaided, 6/9

with 0 D.S./−1 D. cyl. axis 135 degrees. Her vision has slowly improved since the operation just over two years ago, suggesting that she also had an element of amblyopia, which tends to improve spontaneously without occlusion.

The anterior chamber depth is 1·7 mm, the implant is 0·25 mm thick at its thinnest point centrally and there is 1·0 mm of clearance between the back of the implant and the front of the crystalline lens which is perfectly clear.

Case 10 C W, female, aged 10
Bilateral high myopia in a child
This little girl has a very unfortunate pedigree of progressive myopia; several members of her family have become registered as blind before the age of 30 from this cause. At the age of 9 her vision was: Right 6/36 with −11 D.S./−3 D. cyl. axis 20 degrees; left 6/36 with −10·5 D.S./−2 D. cyl. axis 15 degrees. She was falling behind in her work at school and was referred to the contact lens clinic at Moorfields in the hope that a contact lens would provide her with better vision but it was impossible to fit her. A year ago the right eye was fitted with an anterior chamber implant, after a preliminary iridectomy. The result was 6/24 vision unaided, slightly improved with −2 D.S. Apart from a slight horizontal deformation of the pupil this seemed satisfactory and the second eye was similarly treated in May 1960. This implant was fitted with an inferior ledge. The visual result is the same as in the other eye. The functional result has helped her to make excellent progress at a normal school. She already has well-marked degenerative changes at the posterior poles; these may extend and ultimately she may have to be registered as blind. In the meantime it would appear that the bilateral insertion of anterior chamber implants with a concave correction has been helpful to her. Post-operative anterior chamber depth is 1·7 mm.

I think her eyes are continuing to grow and that her present implants may well become too short and insufficiently powerful within the next year or so and they may have to be changed for longer and more concave implants.

This is the only case of bilateral correction of a myope in my personal series of 302 patients in contradistinction to Barraquer's figures where, out of 411 cases, 239 were myopic. He did not state how many of these were unilateral and how many bilateral, but I understand that a majority were bilateral (Barraquer 1959, Barraquer 1960 personal communication). I do not think that bilateral myopes should be fitted with bilateral anterior chamber implants unless special circumstances exist as in Case 10.

Case 11 L V, female, aged 9 (Figs 2, 7A & 7B)
Albinism and high myopia in a child. Anterior chamber implant used to provide artificial iris and correction of myopia
Prior to insertion of implants right and left vision was 3/60 with −18 D.S./+4 D. cyl. axis 90 degrees. She was struggling at an ordinary school but was greatly handicapped visually. In May 1960, a fortnight after the usual iridectomy, the right eye was fitted with an anterior chamber implant with a blue opaque haptic portion and a 4 mm optic bearing a myopic correction. As a result, photophobia was eliminated, nystagmus was less and vision was 6/36 unaided not improved. Understandably she began to use this eye to the exclusion of the left, which developed a marked convergent squint and I felt that there was no alternative but to treat the second eye in the same way. In August 1960 this was done with a similar visual result. Inserting these implants has increased her astigmatism from 4 to 6 dioptres but the vision is not improved with a cylindrical spectacle correction, so presumably the effect of this astigmatism has been lessened by reducing the size of the optic to 4 mm diameter. She is getting along very much better at school since these operations. Post-operative anterior chamber depth is 1·9 mm right and left.

Case 12 W F S, male, aged 48 (Figs 3 & 4)
Left traumatic mydriasis treated with an implant with coloured opaque haptic
In October 1959 he was struck in the left eye by a piece of wood. This caused a choroidal rupture above the disc, traumatic mydriasis, a slight subluxation of the lens and a few non-progressive lens opacities. Vision was 6/24 not improved, and in the open air he had to close his left eye because of photophobia. In October 1960 an anterior chamber implant with 4 mm plano optic surrounded by a blue opaque haptic was inserted. (To match a green or brown iris implants with green or brown haptics would have been used: Figs 7C & 7D.) Left vision is now 6/9 with −1 D.S./−2·5 D. cyl. axis 15 degrees; the photophobia is much less and the appearance of the eye is almost normal. The usual preliminary iridectomy was done before the implant was inserted but where the iris sphincter has been ruptured, as in this case, post-operative pupil block is unlikely to occur and it may be that a preliminary iridectomy is not necessary in this type of case. He suffers from post-encephalitis parkinsonism which ruled out a cosmetic contact lens because he could not carry out the necessary manipulations. He is not a good witness but he does appear to have benefited from this operation.

Post-operative anterior chamber depth is 1·9 mm. Anterior chamber implant thickness is 0·5 mm. Anterior chamber implant to crystalline lens is 0·5 mm.

Case 13 C J E, male, aged 40
Anterior chamber implant used for cosmetic purposes: High myopia with blind, ugly left eye. Left artificial pupil
Right and left refraction was −16 D.S./−1·5 D. cyl. Four years ago a left retinal detachment was unsuccessfully operated upon elsewhere. Three years ago a detachment developed in the right eye which, happily, was replaced at Southend and it has remained *in situ* ever since. The left eye developed an ugly complicated cataract and some divergence. The patient was dissatisfied with the appearance of this eye and in September 1960 an occlusive implant was fitted to provide him with a more normal-looking pupil. The black optic has a 5 mm diameter. The implant has also an inferior ledge. After the preliminary iridectomy he

Fig 2 **Case 11** *Albino eye with anterior chamber implant used to provide artificial iris. 4 mm optic and blue opaque haptic*

Fig 3 **Case 12** *Traumatic mydriasis before operation*

Fig 4 **Case 12** *Traumatic mydriasis. Anterior chamber implant used to provide artificial iris. 4 mm optic and blue opaque haptic*

Fig 5 *Mr Zorab's case. Before operation*

Fig 6 *Mr Zorab's case. Artificial pupil* in situ

had a brisk hæmorrhage into this eye which took some time to absorb, thus illustrating the importance of doing this iridectomy as a separate preliminary procedure. Post-operative anterior chamber depth is 1·7 mm.

Mr Edward Zorab has kindly allowed me to include pictures of one of his patients (Figs 5, 6 & 7F). When these pictures were taken the pupil was still slightly dilated from atropine. Normally no part of the cataract is visible behind the black pupil. I congratulate him on such an excellent result.

If the cosmetic problem is an ugly cataract and a discoloured iris, a further refinement is possible by the provision of an implant with black optic and coloured opaque haptic, as in another case where the healthy eye was blue and an accurate match was obtained with a suitable implant in the other eye (Fig 7E).

Case 14 Mr B, aged 60

Anterior chamber implant used for a mechanical purpose: Insertion of an anterior chamber implant prior to penetrating keratoplasty in an aphakic eye

In 1956 a right extracapsular extraction unfortunately

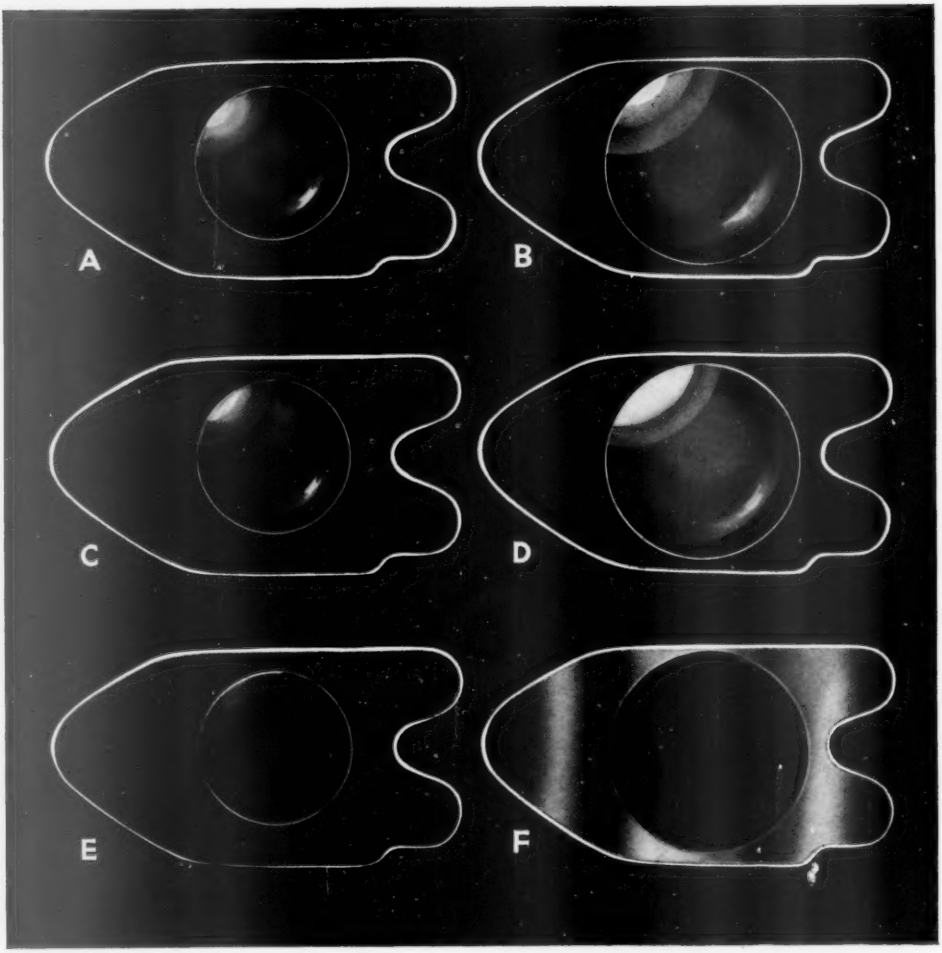

Fig 7 *Anterior chamber implants.* A, *blue opaque haptic and 4 mm clear optic (as used in albino eye).* B, *blue opaque haptic and 6 mm clear optic.* C, *green opaque haptic and 4 mm clear optic.* D, *brown opaque haptic and 6 mm clear optic.* E, *artificial iris in blue with artificial pupil (4 mm black optic).* F, *the artificial pupil, clear haptic and 6 mm black optic*

resulted in vitreous filling the anterior chamber, thus setting up attacks of secondary glaucoma and some endothelial corneal dystrophy. In 1957 an anterior chamber implant (which carried an aphakic correction) was inserted with the object of keeping the vitreous away from the cornea and relieving the attacks of secondary glaucoma. However, this implant was too short, moved about the anterior chamber and made the situation worse. In 1958 it was removed and replaced with a longer implant which proved stable. The attacks of secondary glaucoma ceased and there was slight clearing of the cornea but the vision was only hand movements. In 1959 a 5 mm penetrating keratoplasty was performed, held in position by cross-over sutures. This graft failed to clear. In March 1960 a 7 mm lamellar keratoplasty was carried out and in November 1960 a 6 mm perforating graft was performed, secured by nine direct sutures. There was a slight post-operative rise in intraocular tension for which anterior flap sclerectomy and peripheral iridectomy was performed in December 1960. In spite of the amount of surgery inflicted upon this cornea the graft looks promising.

Conclusions

(1) I have tried to show cases which illustrate some of the uses of the various models of anterior chamber implants for whose development I have been personally responsible.

(2) Special emphasis has been laid on the correction of uniocular aphakia in cases not suitable for contact lenses because I consider this to be the most important use to which anterior chamber implants can be put at the present time.
(3) The cases have been selected to illustrate that the possession of an anterior chamber implant does not unduly restrict the activities of the patient. The only pursuits barred are those like boxing, all-in wrestling and Rugby football.
(4) I attach great importance to the post-operative anterior chamber depth, that is the distance between back of cornea and front of anterior chamber implant centrally. Measurements are taken with the anterior chamber depth measuring device fitted to a Zeiss Opton corneal microscope. Experience shows that a reading of 1·5 mm is adequate; if the reading is 1·0 mm or less the anterior chamber implant should be removed because of the danger of endothelial corneal dystrophy arising later.

Acknowledgments: Many of my patients have been referred by colleagues to whom I am grateful. I am also grateful to Dr G G Stewart, County Medical Officer of Health, who has kindly provided me with access to a number of cases registered with the Essex County Council as blind or as partially sighted, and to Mr Keith Lyle for his assistance in the management of the muscle-balance problems presented by some of these longstanding cases of uniocular aphakia after correction of the aphakia by the implant. I am also indebted to Rayners Limited for the excellent implant service they have provided.

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Mr P M Caudell (*London*) emphasized the necessity for close collaboration between the ophthalmologist and the technician responsible for the manufacture and supply of the intraocular lens. He mentioned the optical state of the eye before implant surgery and stressed the fact that this must be carefully examined with particular attention paid to the vertex distance of the spherical trial lens from the cornea and the state of the other eye.

He recommended the measurement of anterior chamber depth both before and after implant surgery and, in the selection of the type of implant to be used, drew attention to the large range of different shapes now available and suggested that the most suitable be chosen for the eye, not the eye made to fit the implant.

Mr Caudell concluded by remarking that where large numbers of successful cases were recorded, as in Mr Choyce's paper, some part of the success had been due to a very close examination of both the surgical and the mechanical problems by the surgeon and his technician working together.

Mr Harold Ridley (*London*) said that perhaps the most dramatic patient was the myopic child with albinism (Case 11) into each of whose eyes Mr Choyce had inserted partly opaque anterior chamber lenses. What was more important, however, was that recent advances in intraocular acrylic lens surgery now made it possible to restore sight to a child with traumatic cataract or even, in suitable cases, to one suffering from uniocular cataract of developmental origin.

Mr Choyce had produced some innovations of his own and was responsible for the production of lenses which were coloured for cosmetic reasons or to exclude unwanted light. He was to be congratulated on being the first to employ intraocular lenses to facilitate full-thickness grafts in eyes which had previously undergone cataract extraction.

Mr T A Casey (*London*) referring to the value of anterior chamber lenses in aphakic grafting, said that the main problems were loss of vitreous during the operation, and vitreous contact with the graft post-operatively. Thomas (1955) had described a spatula which he inserted in a separate corneoscleral incision. The second method was the use of a Flieringa ring combined with profound reduction of the intraocular pressure by intravenous urea. These methods had the disadvantage that vitreous might be in contact with the graft after operation, particularly if the vitreous face had been broken.

Barraquer (personal communication) aspirated vitreous through the pars plana before cutting the graft.

For the past eighteen months the practice in the Westminster Hospital had been the insertion of an anterior chamber implant as a first stage operation, followed later by keratoplasty. This had the advantage of preventing vitreous loss during operation, and preventing vitreous contact after operation. The procedures of implant insertion and keratoplasty were performed in the usual fashion.

(Five cases were demonstrated.)

REFERENCE

Thomas C I (1955) The Cornea. Springfield, Ill.; p 1075

Mr M J Roper-Hall (*Birmingham*) asked Mr Choyce if the axis of astigmatism was related to the position of the corneal wound made to insert the intraocular lens or whether it was related to the axis in which the lens itself was placed. What was the expected astigmatism following the insertion of a lens?

Mr A Lister (*London*) asked if Mr Choyce could tell him anything of the possible complications of an operation for the insertion of an acrylic implant into an anterior chamber and their incidence.

Mr M Gilkes (*Brighton*) said that, while he did not oppose the use of intraocular acrylic lenses, he felt that, despite the results demonstrated, this procedure was still not without its hazards. He and a number of his colleagues had found that the complication rate was not low, perhaps even of the order of 20–25%, in

approximately 50 cases. In his own series there had been 2 cases where, despite an apparently completely successful surgical result, the vision had gradually deteriorated from 6/6 or 6/9 to 6/24 or lower with no obvious cause. In others there had been various complications including prolonged uveitis and late secondary glaucoma, necessitating removal of the lens. He felt that the indications and contraindications were by no means fully established and would like to hear more about them.

The question of complications was important. Was it always justifiable to hazard a good reserve eye, after some traumatic lesion, by undertaking additional surgery purely for the purpose of regaining binocular function, which in many patients was not appreciated? Apart from this there were the social and economic factors of multiple and delayed operative procedures to be taken into account. Where the possibility of amblyopia supervening arose, this became of overriding importance.

In one of his own cases monocularity over ten years had resulted in no particular disability. An acrylic lens was inserted; after an initial satisfactory result with 6/6 vision, maintained for about three months, secondary glaucoma set in. Two procedures directed to this were without avail and eventually the lens had to be removed. The eye, which had seen 6/6 with aphakic correction, now saw only 6/12. At one time sympathetic ophthalmia had seemed likely to ensue.

Mr T Keith Lyle (*London*) said he had visited Mr Choyce in Southend two years ago and had seen him operate and had learned many practical points about the technique. He felt that considerable experience was needed in work of this kind and that it was best done by those who were prepared to give the matter considerable time and thought.

Professor Norman Ashton (*London*) said that he had now examined pathologically four eyes (two from post-mortems) in which anterior implants had been inserted, and had found a marked degree of atrophy and distortion in the parts of the iris upon which the acrylic implant rested. In one case this had developed in only six weeks. On this evidence it appeared uncertain whether the iris bed would continue to support the implant in position with the passage of years. Until this question had been resolved by long-term observations on existing cases, he felt that the exact value of this operation must remain in doubt.

Mr Choyce, in reply to Mr Roper-Hall, said that the axis of astigmatism was related to the position of the corneal wound and not to the axis of the implant.

With regard to possible complications, Mr Choyce referred Mr Lister to his other publications (in particular to Choyce 1960*a*, p 430), which described complications occurring within five months of implant insertion. He added that so far he had not seen delayed (up to five years) complications in cases which at five months had appeared satisfactory in every respect. He was sure that all implant cases should be kept under regular observation, at least once every twelve months, so that the surgeon could remove an implant if he was not satisfied with it and felt that its continued presence in the eye might result in irreversible complications.

Mr Choyce was sorry to hear that Mr Gilkes and his colleagues had encountered a 20–25% incidence of complications, but felt he could not comment further without knowing how many cases were involved, the pre-operative state of the eyes and other data. Mr Choyce had had his worries with his first few cases, but had found that with increasing experience in the selection of cases, the surgical technique and the post-operative care, complications had markedly declined and results correspondingly improved. The incidence of serious complications had been 22% in his first 100 cases and had declined to 3% in the third 100 cases.

Anticoagulants in the Treatment of Retinal Vein Thrombosis

by B Thorne Thorne MB MRCP DO (*Brighton*)

Thrombosis of the central vein of the retina is familiar to all of us and it is evident, from the amount of congestion and hæmorrhage caused by the obstruction to the venous return, that a considerable degree of damage is going to be caused to the retinal tissues. Also, the condition is sufficiently common and the prognosis for vision is usually so poor, that if there is a method of treatment which can in some cases improve the poor prognosis, or can prevent the full picture of thrombosis occurring, that treatment will obviously be of some value.

Anticoagulants have been used in the treatment of this condition for a number of years, but until fairly recently they have not been in very general use, partly because of the difficulties in controlling the effects of the drug, and partly because the results of treatment have not been particularly encouraging.

In the last few years there have been reports of the value of the newer types of anticoagulant drugs in the treatment of retinal vein occlusion but, in my experience, this form of treatment is the exception rather than the rule. This may be due to the fact that the progress of the condition is too variable, making assessment of the value of any form of treatment too difficult, or because the giving of anticoagulants creates problems of its own, both for the patient and the doctor (though these problems are sometimes exaggerated). Or is it that this form of treatment does no good?

Lister & Zwink (1953) concluded, from their series of 13 cases, that the final visual acuity of an eye affected by venous occlusion was approximately the same as the visual acuity at the outset. They considered that anticoagulant therapy as then available was not justified; one reason being that there is considerable difference of opinion whether the obstruction of the vein is in fact due to thrombosis or to endothelial or intimal

thickening. This problem has still not been resolved.

Gayer Morgan (1955) stressed the value of the use of anticoagulants in the prophylaxis of retinal vein thrombosis, illustrating this point by reference to cases in which dilated or tortuous retinal veins were noted in the good eye, the other eye having been affected by a full-blown thrombosis. Stephenson (1956) reported some success in treating cases of partial thrombosis of a retinal vein, but considered that anticoagulants were of no value in cases of complete thrombosis.

Vannas & Orma (1957), reporting on patients with central vein occlusion and those with main branch occlusion, stated that those treated with anticoagulants, mostly heparin and what they term antisclerosis therapy, did much better (59% in the treated) than the control group (14%) both from improved vision and field. Also fewer in the treated group developed secondary glaucoma. My cases certainly do not attain the high percentage of success which these workers obtained.

The association of retinal vein occlusion and primary glaucoma has been recognized for many years. Redmond Smith (1955) drew attention to the occurrence of central retinal vein occlusion, as a complication of a pre-existing glaucoma, and Dobree (1957), in a series of 200 cases of primary glaucoma, found obstruction to the venous return at the disc in 15·5%. More recently Vannas & Tarkkanen (1960), using tonography and provocative tests in a series of 71 patients with central vein occlusion, found 42% to have primary glaucoma in both eyes, and that those patients treated with long-term anticoagulant therapy had a better final visual result than those untreated.

About two years ago, I was stimulated to see if it were possible to tell, in my hands, if anticoagulant therapy was of any use. At the outset I must say that there is nothing particularly new in this short paper. It describes the results of treatment with anticoagulants of a series of cases of retinal vein occlusion, and compares these results with a control series treated without anticoagulants. I had intended to treat alternate patients but in practice this was not possible owing partly to the difficulty of arranging for the necessary prothrombin level tests to be done, because of the distance of the patients' homes from the laboratory (and I was anxious to treat all cases as out-patients) and partly to the wish of some of the patients' doctors that this form of treatment should not be given. So the control cases and treated cases were selected more by chance, but in effect I do not think that this has weighted the evidence for or against this form of treatment, except that it has resulted in only a few of the cases with branch vein occlusion being in the treated group.

Method of Treatment

The drugs used are heparin, phenindione (Dindevan) and warfarin (Marevan). Heparin is used only where the thrombosis is probably of very recent origin, i.e. under twenty-four hours. It is used in doses of 7,500–10,000 i.u. intravenously, six-hourly for one to two days.

The same day or next day, the patient is started on Dindevan, initial dose of 150 mg on the first day, 100 mg on the second day and a maintenance dose of 50–150 mg a day. Dindevan acts fairly quickly in lengthening the prothrombin time (36 hours). The aim is to maintain a level of two-and-a-half times the normal, i.e. a prothrombin time of 30 seconds.

The following factors must be taken into account in assessing the dosage: (1) Weight – generally the heavier the patient the larger the dosage. (2) Ill patients require smaller dosage. (3) The older the patient the smaller the dose necessary. (4) Deficient renal function, leading to delayed excretion of the drug, indicates smaller dosage.

Patients are warned not to take salicylates or aspirin while on anticoagulants. Liver disease is an absolute contraindication. I have left the regulation of the dosage entirely to the pathologist, and I am much indebted to Dr J Horley for his help. Patients who show intolerance to Dindevan in the form of diarrhœa or dermatitis are changed to Marevan 3–5 mg b.d.

The treatment is continued for many weeks, even up to a year or more. In this series I have found little further improvement after six months, but in a number of cases I have continued with treatment after this, with the idea of preventing a thrombosis occurring in the fellow eye, where there has been well-marked sclerosis of the retinal vessels and some evidence of venous congestion.

For the first few weeks it is necessary to estimate the prothrombin time of the patient's blood once or twice weekly, and as the treatment becomes stabilized, the interval between blood tests can be lengthened to a month.

Assessment of Results

The assessment of the results of treatment in this condition is difficult, owing to the variability in degree of recovery of vision, but the following criteria seem to be the most useful for this purpose: (1) Visual acuity, distance, and if possible, reading. (2) Fields and Amsler charts. (3) Absorption of hæmorrhages. (4) Development of thrombotic glaucoma.

For the purposes of this paper and for reasons of brevity I have condensed all these factors together in estimating whether a case has improved, has shown no change or has become worse.

Material

The series consists of 50 consecutive cases of retinal vein occlusion seen and treated by me between July 1959 and September 1960. This number shows that the disease is fairly common in our practice. 17 (34%) were male and 33 (66%) female. Duke-Elder (1940), however, gives the incidence between the sexes as equal.

The age groups are shown in Table 1, and they conform to the usual pattern.

Table 1
Age and Sex

	40–49	50–59	60–69	70–79	80+	Total
Male	4	1	5	6	1	17
Female	3	4	10	13	3	33
Total	7	5	15	19	4	50

Twenty-eight (56%) of the patients had a diastolic blood pressure of 100 mm Hg or over; a few more had systolic pressures over 200 mm Hg, but diastolic readings below 100 mm Hg. Only 4 (8%) of the cases had undoubted primary glaucoma in the fellow eye, but this figure is probably too low, as tonography and detailed provocative tests were not carried out in the majority of cases.

Results (Tables 2, 3 and 4)

Table 2
All cases

	Anticoagulants (22)		*Controls* (28)	
	Cases	%	*Cases*	%
Improved	8	36	8	28·5
No change	11	50	12	43
Worse	3	14	8	28·5

Table 3
Central Vein (29 Cases)

	Anticoagulants (17)		*Controls* (12)	
	Cases	%	*Cases*	%
Improved	6	35	3	25
No change	9	53	6	50
Worse	2	12	3	25

Table 4
Branch Vein (21 Cases)

	Anticoagulants (5)		*Controls* (16)	
	Cases	%	*Cases*	%
Improved	2	40	5	31
No change	2	40	6	38
Worse	1	20	5	31

Three cases out of the 12 in the central vein control series developed thrombotic glaucoma, whilst none of the 17 treated cases did so.

Complications arising possibly directly from the anticoagulant therapy were:

(1) *Hæmorrhage:* Hæmaturia, 3 cases. Epistaxis (slight), 1 case. Skin bruising, 2 cases, 1 of which also had hæmaturia and the treatment had to be stopped after six weeks. Vitreous hæmorrhage, 1 case; possibly due to the thrombosis itself; it cleared within three months without the dosage being reduced.

(2) *Diarrhœa*, severe in 1 case, slight in 3; all stopped on changing to Warfarin.

(3) *Indigestion* occurred in a few cases but in none was it severe.

(4) *Dermatitis*, slight in 2 cases.

Recently, a few patients have volunteered the information that they have a dry mouth and nasty taste in their mouth when on Dindevan, but not on Marevan.

Conclusions

The numbers in this series may not be sufficient to form a very firm opinion as to the value of anticoagulants in retinal vein thrombosis, but I think the results do show that those patients having the treatment are more likely to improve than those without it, and are also less likely to suffer from thrombotic glaucoma. Only one patient in the whole series actually developed venous occlusion in the second eye, and although treated with anticoagulants she has done badly. It is not possible, on the data available here, to say whether or not this treatment can prevent a partial or suspected thrombosis from becoming a complete occlusion, but I maintain that the treatment of such cases is worth doing, and will not do harm.

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Mr E S Perkins (*London*) agreed that it was important to decide on the value of anticoagulant therapy. He had recently treated a case of partial central vein thrombosis with anticoagulants for one month, the vision in the affected eye remaining at 6/18. Two weeks after stopping treatment – owing to difficulty in controlling the prothrombin level – a further thrombotic episode occurred, reducing vision to 6/60. It seemed likely that had the treatment been continued for a longer period this relapse would have been prevented.

Mr Perkins asked Dr Thorne Thorne for what length of time anticoagulant therapy should be given in these cases.

Mr E F King (*London*) asked if Dr Thorne Thorne had at any time noticed, in a retinal venous thrombosis, an increase of hæmorrhages following anticoagulant therapy.

Mr Redmond Smith (*London*) pointed out that it was vital to know whether the apparent better results in the treated groups had been subjected to any statistical tests. Although the numbers were small, it was quite possible that the differences might be significant.

Mr J Primrose (*London*) stated that one of the first principles of medicine was that the treatment should not do the patient harm. Mr King had already mentioned the risk of further hæmorrhages resulting from anticoagulant treatment of central retinal vein thrombosis. Mr Primrose reported a case he had under such treatment who developed further hæmorrhages and a fulminating glaucoma, from which the patient lost his eye.

Mr T Keith Lyle (*London*) thought one of the greatest values of the treatment described by Dr Thorne Thorne was the prevention of thrombotic glaucoma.

He asked Dr Thorne Thorne if, in cases of tributary thrombosis, he had differentiated between those involving the nasal tributaries and those of the temporal tributaries. Where the macular region was spared, as in the case of thrombosis of either of the nasal tributaries, the central visual acuity was obviously likely to be unaffected.

Mr John A Chivers (*Orpington*) stated that he had at present a patient under treatment with a partial thrombosis of the central retinal vein in an aphakic eye, in which he had noticed that the hæmorrhages had increased as soon as the anticoagulation treatment with heparin and Dindevan was begun, and that in this case he had reduced the Dindevan so that coagulation of the blood was not reduced fully, but only to about 17% (Owren's technique – normal therapeutic range 10% to 25%). After this no new hæmorrhages appeared and after a fortnight's treatment the corrected vision improved to 6/36.

Dr Thorne Thorne, in replying to Mr King, stated that in at least one patient the hæmorrhages increased after starting anticoagulants; but increase of hæmorrhages had occurred more frequently in cases not having anticoagulants, and he thought that this sequel was due to the disease rather than to the treatment. This also answered Mr Primrose's point.

In answering Mr Redmond Smith's question, Dr Thorne Thorne stated that a statistical analysis had been obtained; the result of this had shown that there was little difference in the outcome of the treated and the control groups. However, the statistician had commented that the conclusions drawn were cautious and not open to criticism from the statistical aspect.

In reply to Mr Keith Lyle, Dr Thorne Thorne said that a review of the cases had shown that the majority of branch vein thromboses had been of the superior or inferior branches, thus involving the temporal and nasal tributaries; only two of the cases were of the nasal branch alone.

The Clinical Value of Ophthalmodynamometry

by Vernon H Smith FRCS (*Manchester*)

Recent experience has suggested that ophthalmodynamometry has a useful part to play in the diagnosis of cerebrovascular and retinal vascular disease (Liversedge & Smith 1961). The present report is based on experience in the dynamometry clinic at the Manchester Royal Eye Hospital during the past year. During this period 273 patients have had dynamometry performed on them, of whom 145 were referred from the Manchester Royal Infirmary, and 128 from the Manchester Royal Eye Hospital. Among them there were 39 with carotid occlusion and 58 with central retinal artery occlusion.

Theoretical Considerations

Ophthalmodynamometry provides a measurement of the pressure in the ophthalmic artery in terms of the grams of extraocular pressure that are required to produce a maximal pulsation at the disc for the diastolic pressure, and the moment that this disappears for the systolic pressure. These figures are not to be regarded as a true measurement of the pressure in the ophthalmic artery, but are only of value for comparison between the two eyes of one patient. A difference in the ophthalmic artery pressures as shown by dynamometry may be expected in the following conditions:

(1) *Carotid occlusion:* A fall in pressure in the artery distal to the site of occlusion might be expected. This would be followed by a corresponding fall in the ipsilateral ophthalmic artery. Dynamometry would detect this, but would have no localizing value for the actual site of the obstruction. Furthermore, if the collateral circulation was well developed – as in a longstanding case, then it is possible that this may have completely compensated for the occlusion and dynamometry would be normal.

Case 1 Mr H E, aged 60

In 1955 this patient was diagnosed as suffering from stenosis of the left internal carotid artery, and at that time a carotid angiogram (Fig 1) showed a stenosis of the carotid just above the bifurcation with good flow up the external carotid and a rich anastomosis between the branches of this artery and those of the ipsilateral ophthalmic artery. Ophthalmodynamometry performed almost five years later gave exactly equal results on both sides.

Dynamometry would also be negative in cases where the obstruction to the flow was as yet not sufficient to cause a drop in pressure.

Fig 1 **Case 1** *Carotid angiogram*

Case 2 Mr J A, aged 54
This patient was diagnosed as suffering from stenosis of the internal carotid artery, and the angiogram shows this well (Fig 2). It also shows good filling of the carotid distal to the stenosis, indicating that a considerable amount of blood was still passing up this vessel. Ophthalmodynamometry failed to reveal any significant difference between the two ophthalmic artery pressures. Surgical disobliteration was performed by Mr K Bloor, and at operation direct pressure readings were taken from above and below the obstruction before it was removed. These were the same, showing that dynamometry had truly represented that there was no fall in pressure across the stenosis.

An apparent false negative will also occur in cases of bilateral carotid occlusion. Here both sides may show an equally reduced pressure. The diagnosis may be suspected by the low level of the reading compared with the blood pressure. Although it has been stressed that dynamometry does not provide an accurate measurement of the ophthalmic artery pressure, the readings follow the blood pressure in a general way. For example, a patient with a blood pressure of 200/100 would probably give a dynamometry reading of 150/90 and a systolic reading of less than 100 from both eyes would be very suggestive of bilateral carotid occlusion.

(2) *Obstruction in the ophthalmic and central retinal arteries:* Obstruction of the central retinal artery that causes a reduced pressure or no pulsation at all on dynamometry may completely mask a co-existing carotid occlusion on the same side. Fortunately not all cases diagnosed as central retinal artery occlusion have an organic blockage in the vessel, and so this does not apply.

Fig 2 **Case 2** *Carotid angiogram*

Blockage of the ophthalmic artery is more difficult to detect during life, but is probably rare. Carotid angiography only outlines the vessel in approximately half the cases, and the vessel is not always studied at necropsy. If collateral circulation through the ophthalmic-external carotid pathway was poorly developed, occlusion of the ophthalmic artery could give rise to a reduced pressure on ophthalmodynamometry.

Case 3 Mr N W, aged 61
This patient was diagnosed as suffering from right internal carotid occlusion in March 1960 and dynamometry at that time showed a considerable reduction in pressure in the right ophthalmic artery. Surgical disobliteration was undertaken but the patient subsequently died. Necropsy (Dr P O Yates) showed that both ophthalmic and central retinal arteries were healthy and had never been thrombosed, so that the fall in pressure recorded by dynamometry had been due to carotid occlusion.

The Reliability of Ophthalmodynamometry in the Diagnosis of Carotid Occlusion

False negative results: The cause of these has been discussed above. In the present series of 39 cases of carotid occlusion there were 4 such cases, slightly more than 10%.

False positive results: There were 3 of these, which must be taken in relation to the total of 273 cases studied, less those suffering from carotid occlusion, an incidence of 1·3%.

These cases represent a much more serious problem than the false negatives, as they run the danger of an unnecessary surgical exploration to which indeed 1 of them was submitted.

The 3 cases had many features in common. They were men, aged 27, 28 and 45 years. All had suffered from unilateral transient amaurotic attacks, had a reduced pulsation in their cervical carotid arteries on palpation and had a significantly lowered dynamometry reading on that side. Subsequently the cervical carotid pulsations became equal, they stopped having amaurotic attacks, and their dynamometry readings returned to normal. Carotid angiography was performed on 2 of them, and this was normal.

No reliable diagnosis has been possible in these cases. They present a picture that could be described as retinal migraine. The pathology is a matter for conjecture.

Technique

The technique has already been described in detail (Smith 1960) but certain points may be emphasized:

(1) If the examination is carried out with the patient supine it is quite easy to perform it without any assistant, as the patient can fix on a light on the ceiling. Readings can also be taken with the patient sitting up, a point that will be referred to later.

(2) Every patient should have the pupils dilated, followed by a careful examination of the fundi. Hitherto unsuspected pathology may be discovered.

(3) More than one estimation of the ophthalmic artery pressure is permissible and indeed desirable. It has been stated that, if the end point is missed, the examiner should wait for twenty minutes for the anterior chamber to reform before taking another reading. This is technically correct, but in practice an experimental error of 20% covers any variations that may arise by repeating the readings immediately. In the dynamometry clinic it is customary to take three readings from both eyes. Provided that the same time is taken over the readings from the two eyes they will retain their comparative value; furthermore a patient who is a little apprehensive for the first reading may well become a good subject for the test when it is performed a second and third time. Both eyes are tested alternately. Experience has shown that a true difference between the ophthalmic artery pressures will continue to show itself however often the reading is repeated.

(4) These statements will only hold if an experimental error of 20% is accepted. By that is meant that the lower reading must be more than 20% less than the higher reading to represent a significantly lowered ophthalmic artery pressure on that side. Even so it is sometimes difficult to give an opinion on whether a reading is pathological or not and four patients in this series had to be re-examined on a subsequent occasion before this was possible.

Technical Difficulties

In 9 cases (3%) there were technical difficulties that made the results difficult to obtain or to interpret. Two patients found it impossible to co-operate sufficiently; 3 had too much cataract on one side to allow a view of the disc; 1 patient had vertical nystagmus; 1 showed marked drying of the cornea. One patient had a filtering scar from a glaucoma operation which allowed the aqueous to be forced into the subconjunctival space so quickly that an unreliably high reading was made, and 1 patient had so much calcification in her vessels that no pulsation was visible although blood was clearly going to the retina as the vision with that eye was 6/12.

Contraindications

The list of possible contraindications is long, but 5 patients were considered unsuitable for dynamometry for reasons that only became obvious after the pupils had been dilated: in 2 there were scattered vitreous hæmorrhages, and in 3 there were peripheral retinal tears although the retina was not detached.

CLINICAL APPLICATIONS

General Conditions

Carotid occlusion: Dynamometry is diagnostic in 90% of cases of carotid occlusion, separating them from other conditions that could be included in the same differential diagnosis. It is especially selective with regard to middle cerebral occlusion. There were 26 cases with the latter condition in this series, all with normal dynamometry results.

Surgical disobliteration: Dynamometry provides a means of assessing the success of carotid disobliteration that does not involve the hazards of angiography, which may be high, in the immediate post-operative period. In all, 9 patients on whom dynamometry was diagnostic underwent surgery, and of these 5 were tested again during the immediate post-operative period. The patients tolerated the procedure well, especially as it was not a novel experience.

Vertebro-basilar occlusion: There were 12 cases of extracranial cerebrovascular disease where the carotid arteries were not thought to be significantly implicated. When this diagnosis was suspected an additional procedure was adopted.

Routine dynamometry with the patients supine was performed as usual. This gave normal results in all 12 cases. The patient was then raised to the sitting position and the neck extended fully. Dynamometry was then repeated. Under normal circumstances the pressures obtained are the same or slightly higher than those when the patient is supine. From the 12 patients in whom vertebro-

basilar occlusion was the final diagnosis there was a significant, though equal, fall in the pressures obtained from the two eyes in 2 cases.

As preparation for the angiography: A normal result from ophthalmodynamometry implies either that no significant occlusion of the carotid artery exists or that, if this is so, the collateral circulation has fully compensated for the defect. Under these circumstances the introduction of a needle into the carotid during the performance of angiography is unlikely to jeopardize the cerebral blood supply by damaging the vessel. In this respect ophthalmodynamometry prepares the way for angiography.

Doubtful value in aneurysm surgery: It is unlikely that dynamometry can be of assistance to the neurosurgeon dealing with this problem. It has been suggested that dynamometry be used to assess the probable result of ligature of the common carotid by performing the technique while the carotid was manually compressed.

Case 4 Mrs M D, aged 67

This patient had an aneurysm on the right posterior communicating artery. Dynamometry gave a normal equal result. When the right common carotid artery was manually compressed so that the superficial temporal pulse was obliterated there was a slight fall in the dynamometry reading on that side. This reduction was within the limits of experimental error. When dynamometry was performed on the left eye and the left common carotid occluded there was a most significant drop in the dynamometry reading. The implication from these results was that ligation of the common carotid on the side of the aneurysm would not produce a significant fall in pressure in the carotid circulation. This was not so. Ligation of the right common carotid produced a considerable fall in pressure distal to the ligature as was shown by direct pressure measurements at the time of operation. This was also verified by dynamometry in the post-operative period, when a corresponding reduction in pressure was found on the ligated side.

The technique clearly has little value as a means of assessing the probable result of common carotid ligation. It is possible that more accurate results may be obtained by performing it at the time of operation, but it clearly cannot be as accurate as direct pressure measurements.

Indeed it is only in the post-operative period following carotid ligation that the test may have any value in that it provides a means of checking if any recanalization of the ligated vessel has taken place. It must be recalled that a rise in the dynamometry reading at this time may be due to development of the collateral circulation.

Local Ocular Conditions

Central retinal artery occlusion: Dynamometry allows fresh insight into the pathology of this condition. There were 58 cases with a clinical diagnosis of central retinal artery occlusion, but only 23 of these (40%) were actually thrombosed, thus giving no pulsation on dynamometry. The remaining 60% were not in fact occluded. Of these 27 (46%) pulsated to as high a pressure as did the other eye. In other words dynamometry was normal so far as comparison of the pressures was concerned, although the amplitude of the pulsation was often less than on the normal side. In the remaining 8 cases (14%) the pulsation was at a significantly reduced pressure compared with the normal side. This information about the state of the circulation can only be obtained by dynamometry, and apart from its intrinsic importance has considerable bearing on the prognosis and treatment. Needless to say the only patients who showed any visual recovery were those whose central retinal artery pulsated.

This problem is at the moment under active investigation in the Department of Neurology at the Manchester Royal Infirmary and at the Manchester Royal Eye Hospital.

Central retinal artery branch occlusion: This seemed to be less common than occlusion of the main trunk. Nine cases have been studied, and only 2 were actually occluded. It was often difficult to be certain how far down the vessel the pulsation passed in the remaining 7 cases. Frequently it could be seen passing an obvious constriction in the lumen.

Central retinal vein thrombosis: This group is of special interest. So far only 9 cases have been studied, but there is dynamometric evidence of coexisting central retinal artery occlusion in 5 and of arterial branch occlusion in a sixth. Two of these cases had no pulsation on dynamometry, and in the remaining 3 the pulsation was of grossly reduced amplitude as it was in the case of arterial branch occlusion.

This is a small number of cases but it does raise the possibility that occlusion of the central retinal artery and vein may co-exist far more frequently than is at present suspected. This joint diagnosis can only be made with certainty by ophthalmodynamometry.

Acknowledgments: It is a pleasure to thank the many consultants at the Manchester Royal Eye Hospital and Manchester Royal Infirmary who have allowed ophthalmodynamometry to be performed on their patients and who have permitted consultation of their records. In particular the author is indebted to Dr F R Ferguson and Dr G E Smythe, Department of Neurology at the Manchester Royal Infirmary, and to Mr A Stewart Scott, Manchester Royal Eye Hospital, for their encouragement and advice.

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Section of Orthopædics

President A L Eyre-Brook MS

Meeting March 7 1961

(continued from September 'Proceedings' p 824)

Secondary Carcinomatous Deposits in Bones
R C L Feneley MB (for G O Tippett FRCS)

Mrs H, aged 42 years, admitted to hospital on 20.12.56 on account of increasing pain in the lumbar region. The pain started six weeks previously and was of constant dull aching character with no radiation to the legs. Three weeks before admission the pain, following a fall, became so severe that she had to go to bed. There was no loss of weight.

On admission the patient was noted to be thin and pale. In the left breast there was a large irregular hard lump attached to the skin over a small area. This lump had been growing during the past two years. X-rays showed multiple areas of rarefaction in the lumbar vertebræ and pelvis (Fig 1), femora, scapulæ, humeri, ribs and skull. Hb 48% (8·0 g %); W.B.C. 6,800 with a marked shift to the left; E.S.R. 70 mm in one hour (Wintrobe).

Marrow biopsy (5.1.57) showed the presence of epithelial cell carcinomatous plaques.

8.2.57: Bilateral adrenalectomy and oophorectomy. The prognosis appeared to be hopeless but within one week there was relief of the backache. The patient was discharged from hospital on 24.3.57 on an oral dose of 50 mg cortisone daily. Histological section of both ovaries and adrenals showed secondary carcinomatous deposits.

The patient was followed up regularly and continued to make very satisfactory progress. X-rays in August 1957 showed recalcification of the lumbar spine and pelvis and the secondary deposits were smaller. In February 1961 the patient was well and putting on weight. She had no pain. X-rays showed almost normal bony texture of the lumbar spine (Fig 2), pelvis, ribs and femora. However, those of the skull showed minimal changes compared with 1956 and there was partial collapse of the bodies of T7 and 11. The lump in the left breast had disappeared.

Fig 1 *Pre-operative radiograph*

Fig 2 *Radiograph taken four years after operation*

This patient shows a remarkable recovery and apparent disappearance of primary and secondary carcinomatous deposits following bilateral adrenalectomy and oophorectomy. Over a period of four years there has been no evidence of advance of the disease.

POSTSCRIPT (13.7.61): The patient was readmitted to hospital on 5.7.61 with a partial paraplegia following further collapse of her thoracic spine.—R C L F

Meeting April 11 1961

Paper

Multiple Stage Leg-lengthening: Report of a Case of Chondrodysplasia with a Surgical Increase of Ten Inches

by Marshall R Urist MD[1] (*Los Angeles*)

The method to be described in this communication differs from previous operations in that it is a multiple stage procedure which consists of implantation of cylindrical bone blocks, produces the increase in leg length in small increments over a period of years, and allows time for growth and adaptation of the soft parts. The success of the procedure depends upon the capacity of the growing skeleton to form an involucrum of new bone around an implant. This is a ten-year progress report of a child with dyschondroplasia (enchondromatosis) involving the ilium, femur, and tibia of the right lower extremity.

Case Report

A female child of Anglo-Saxon-Spanish parentage presented the problem of progressive bowing, deformity, and retardation of growth of the right femur and tibia amounting to 3 cm at 2 years, and 8 cm at 4 years. The child was in excellent general health; extensive medical study revealed no abnormalities other than the regional growth disturbance. No instance of congenital disorder could be found in the family tree in the past two generations. At 5 years, there was tumorous swelling, severe genu varum, anterolateral curvatures of lower thigh and upper tibia, and discrepancy of 12·5 cm in length of the lower extremities. Serial radiographs, between 1 and 5 years of age, revealed speckled, mottled, radiolucent masses expanding the cortex of the lesser trochanter, distal end of the femur, and both ends of the tibia. The growth zones of the fibula and head and neck of the femur were normal. The lateral

Table 1
List of operations

Operation No.	*Date*	*Age*	*Site of operation*	*Procedure*	*Materials used for implantation or graft*	*Months of immobilization in cast*	*Length of implant (cm)*	*Eventual relative increase, external length (cm)*
1	10.10.50	4 4/12	Tibia, proximal metaphysis	Biopsy	–	0	0	0
2	24.11.51	5½	Femur, distal third	Biopsy, osteotomy, implant	Homograft, maternal fibula	3	2·0	2·0
3	8.4.52	6	Tibia, proximal third	Osteoclasis	–	2	0	0·3
4	10.10.52	6 4/12	Femur, proximal third	Osteotomy and implant	Homogenous tibia autoclaved	3	2·5	2·7
5	13.8.53	7½	Femur, distal third	Osteotomy and implant	Homogenous tibia, autoclaved	3	2·5	2·5
6	20.4.54	8	Tibia, proximal third	Osteotomy and implant	Homogenous fibula, autoclaved	4	2·5	2·5
7	26.11.54	8½	Femur, proximal third	Osteotomy and implant	Homogenous tibia, autoclaved	4	3·0	3·4
8	26.11.54	8½	Tibia, proximal third	Onlay bone graft	Autograft, ilium	4	0	0
9	5.1.56	10	Femur, distal third	Osteotomy and implant	Homogenous tibia, autoclaved + new IM nail	4	1·9	1·9
10	8.11.56	10½	Tibia, upper third	Osteotomy and implant	Homogenous fibula, autoclaved	3	2·8	2·8
11	21.5.57	11	Femur, epiphysis, distal, left	Curettage epiphyseal cartilage	Epiphyseodesis	1	–	1·5
12	2.1.58	11 9/12	Tibia, distal third	Osteotomy implant	Homogenous fibula, autoclaved	4	2·5	2·5
13	8.1.59	12 9/12	Femur, proximal end	Osteotomy and implant	Homogenous tibia, autoclaved	4	3·5	3·5
14	29.7.59	13½	Femur, proximal end	Onlay bone graft	Autogenous, ilium	0	–	–
					Total	39	23·2	25·6

[1]From the Department of Surgery, Division of Orthopedics, University of California Medical Center, Los Angeles, California, U.S.A.

aspect of the body of the ilium had a scalloped lateral cortex. Bone survey and biopsies established the diagnosis of dyschondroplasia (Ollier's disease) localized in the right lower limb.

Table 1 summarizes the treatment of the patient, including 14 surgical operations, and the results obtained during the period between 5 and 14 years of age; 23·2 cm were added in 9 stages, and 25·6 cm were obtained in overall correction of discrepancy in leg length by the additional procedure of epiphyseal arrest of the contralateral distal end of the femur at age 11.

Surgical Technique

After exposure of bone for a length of 10 cm, the periosteum and superficial and deep fascia were transected wherever accessible. The medial compartment of the thigh or the posterior compartment of the leg, where the major vessels and nerves are located, were not exposed or dissected, but assumed to be thin enough to permit extension by stretching. Osteotomy was performed between drill holes; muscles and fascia were elongated by the process of repeatedly opening and closing a long lever-arm osteotomy spreader. This instrument was simply a plaster spreader with the tips extended an additional 10 cm, and the handles lengthened 1 meter to gain leverage.

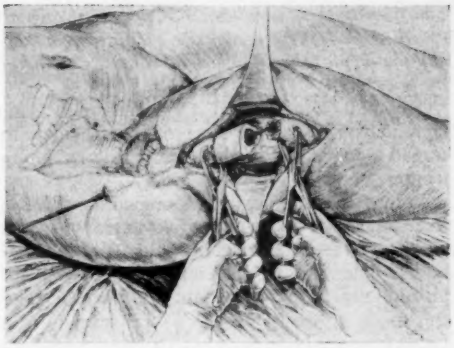

Fig 2 *Drawing of the surgical exposure and method of placement of a cylindrical bone implant to lengthen the leg in increments of approximately 2·5 cm per year*

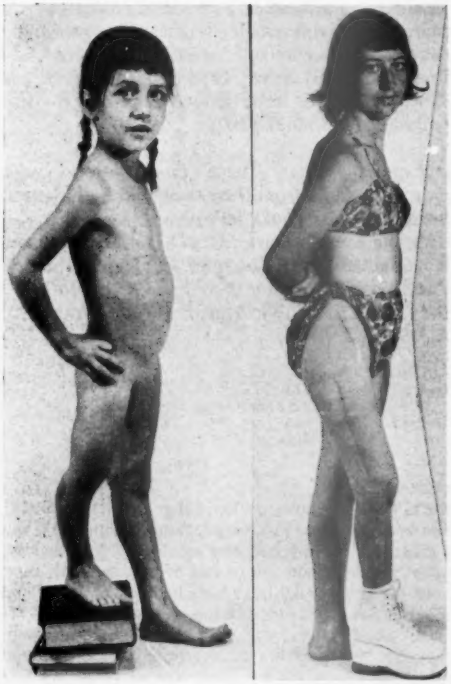

Fig 1 *Photographs of girl at 5 and 14 years of age, before and after 9 leg-lengthening operations on the right lower extremity and one epiphyseal arrest on the left lower femur to produce an overall correction of 25·6 cm*

A B

Fig 3 *Radiographs of the femur:* A, *at age 6¼ years, after Operation No. 4 (Table 1) showing incorporation of bone implanted in distal end of the femur at age 5½ years;* B, *at age 7¼, three months after Operation No. 5, showing placement of another cylindrical implant in distal femur and incorporation of bone implant shown in* A *in the proximal metaphysis*

The osteotomy-spreading and muscle-stretching operation was performed while the intramedullary nail was in place to stabilize and control slipping of the bone ends.

The nail was allowed to protrude just far enough from the end of the proximal fragment to thread a cylindrical implant measuring 2·5 cm in length.

In the femur of a small child, a segment of fibula from an adult made a suitable implant; in the small girl, the distal third of the shaft of the tibia fits the femur. In the adolescent girl, the fibula of an adult male could fit into the marrow cavity and this made it possible to use a 4 in. segment of a fibula from the bone bank both for intramedullary fixation and for the function of the implant, for lengthening the tibia. A block of compact bone was placed in addition between exposed ends of the cortex to maintain the gap of separation and add support. The wound was closed loosely to allow for swelling; a hip spica cast was applied with the flexion of the hip 45 degrees, knee 70 degrees, and the foot in moderate equinus to obtain relaxation of the neurovascular sheath.

Regional circulation: The right foot was slightly warmer than the left, but always within the limits of the normal range; the pulsations were higher and the rates of blood flow were lower on the right than the left.

Neurological function: Sensory perception and motor power in the right leg and foot after each operation were normal. Stretching the nerve in increments amounting to approximately 2·5 cm produced only minor interference with nerve impulse conduction and no EMG evidence of wallerian degeneration.

Post-operative course: Convalescence was surprisingly comfortable. The time interval for healing to the point of removal of the cast was generally three to four months (Table 1).

The process of healing: The radiolucent spots in the bone ends (containing remnants of abnormal epiphyseal cartilage) became replaced and filled with new bone. At the same time, collars of new bone appeared around the bone ends, beneath the periosteum over a distance of 1 to 2 cm on each side of the osteotomy; the bone also increased in density due to activation of the endosteum. Over a period of three to four months, the periosteal and parosteal tissues enveloped the implant in an involucrum; the endosteum probably invaded the interior of the implant. A cylindrical or rectangular block of dense compact bone, containing as much cancellous bone as possible on the inside, gave the osteotomy maximum contact and stability. A wedge-shaped implant as in Operation No. 6, led to early absorption of the implant and insufficient osteogenesis on the long side of the wedge where, presumably, there was strain. A wedge-shaped implant provided an ideal architectural design for correction of bow-leg, but it introduced unsatisfactory local conditions and it became necessary to add an autogenous bone graft as an additional procedure (Operation No. 8) to obtain incorporation of the implant. When the femur was osteotomized and elongated (Operation No. 13) by a third cylindrical implant at the site of two previous operations (Nos. 4 and 7), the proliferative capacity of the host bed was too low to produce union and it was necessary to add an autogenous onlay graft.

Growth: The reaction and adaptation of the femur to the nail was observed at the time of Operation No. 9. The structure of the entire femur had been completely remodelled and the marrow cavity was reconstituted in a new area; the nail was no longer in the centre of the medulla but enveloped in a shell of cortical bone in the lateral posterior wall of the shaft. The increments of growth contributed by the femoral head and the deranged epiphyseal plates were too small to measure. In young rabbits, intramedullary nailing operations were found to inhibit growth of long bones (Behling & Janes 1959), but nevertheless were used for leg-lengthening (Shuliak 1960).

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DISCUSSION

Mr G Osborne (*Liverpool*) said that tibial lengthening had been practised in Liverpool since about 1935, and a great deal of work had been carried out in the subsequent few years on the design of a suitable traction machine (Fig 1). All used Kirschner wires which had the disadvantage of lacking mechanical stability, however elaborate were the devices used to keep them tight. In 1947 workers in Liverpool had commenced using the Edinburgh modified Abbott apparatus and were entirely satisfied with its performance since that time. In this apparatus rigid Steinmann pins were used.

Experience of the operation of tibial lengthening over the last twenty-five years had left them certainly wiser, and at times contrite, although satisfied that the

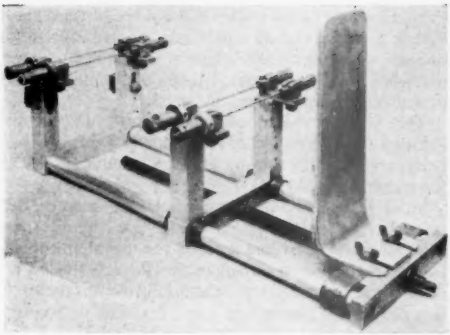

Fig 1 *Distraction machine capable of individual tightening and adjustment of Kirschner wires*

operation had been necessary and beneficial in many cases. Compere (1936) said that 'interest in the successful cases sometimes detracted from lessons which might be learnt from the failures', and there was no doubt that what might appear to be technically feasible was not always a clinically advisable operative procedure even if successful. The operation of tibial lengthening was a mechanical and biological exercise of great magnitude which the human lower limb could withstand successfully only if (1) the pre-operative conditions and indications had been carefully considered, (2) the operative technique was impeccable, and (3) there was a standard of personal post-operative observation and control by the operating surgeon of a very high order.

Complications and the need for experience in dealing with them depended to some extent on the amount of lengthening obtained. Up to one inch of lengthening no complications occurred. Between one and two inches certain definite but avoidable complications might be present, but between two and three inches of lengthening, major difficulties were sometimes encountered which might require the surgeon to abandon lengthening.

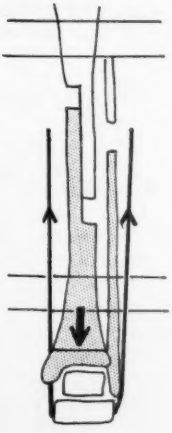

Fig 2 *Effect of distracting force on lower leg. The cartilaginous surfaces of the lower tibial epiphysis, the ankle-joint and the subtaloid joint are compressed between the distracting force thrust distally and the tension of the long tendons which are attached to the foot*

Lengthening of the tibia could produce considerable compression forces on the articular surfaces of the ankle, the subtaloid and midtarsal joints (Fig 2). Thus the dome of the talus could be crushed by this force, or valgus deformity of the foot might occur with upward subluxation of the lower end of the fibula. In Liverpool it had become the practice to divide the fibula in two places and screw the inferior tibio-fibular joint.

The tendo achillis should be lengthened some weeks before the operation, or as a first stage in the operation, to prevent an equinus deformity developing during lengthening, but even so, some deformity of the foot would tend to occur and should be prevented by immobilization of the foot in plaster. As tightening of the tendons occurred, however, particularly between two and three inches of lengthening, excessive pressure might develop between the ball of the foot and the plaster and very careful padding of this area was therefore necessary.

One of the difficulties and dangers which they used to encounter, before using the Edinburgh Abbott apparatus, was of failure to control the bone fragments, but since using this apparatus with its rigid Steinmann pins they had been able to obtain perfect alignment during elongation without danger of pressure atrophy of the skin from the tibial fragments –

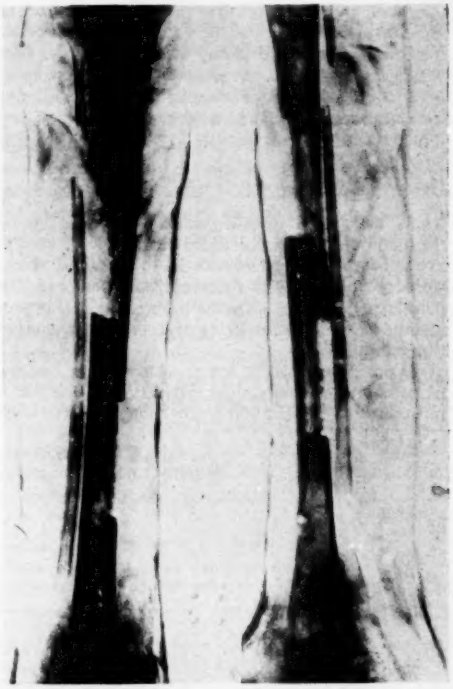

Fig 3 *Case after lengthening. 'Z'-shaped osteotomy performed by multiple drill holes and two inches of lengthening obtained. Now awaiting consolidation in plaster. Note – division of fibula in two places*

either the upper or lower fragment compressing an area of skin from inside.

Lateral popliteal nerve paresis was a very real complication and occurred unless elongation was slow – not more than about one-sixteenth of an inch per day. The cause of the nerve palsy was due to tethering of the nerve by the fascia of the biceps, and also beneath the arch of the peroneus longus.

Indications and contraindications to leg-lengthening: Many patients with a limp attributed it to a short leg and in a proportion of these cases the limp was not due to shortening, but to such factors as gluteal weakness and pelvic obliquity. It was important, therefore, to correct the shortening fully with a special boot as a trial measure before the operation, in order to determine whether there was improvement in the actual function of the leg and particularly that the degree of limp had diminished, before embarking on tibial lengthening.

Tall people could be treated more easily by leg shortening, and in some cases of osteomyelitis or congenital deformity of the leg, such as short femur, it was probable that they should not be subjected to tibial lengthening. The nutrition of the leg needed to be good and poor nutrition or trophic changes were an absolute contraindication. The main indications were poliomyelitis and the short leg of tuberculosis of the hip-joint with premature fusion of the knee epiphyses. The most favourable case was the young adolescent poliomyelitic who had shortening mainly below the knee with a fair amount of paralysis for which he wore an iron (Fig 3). If the tibia were then lengthened two inches he would be able to wear an ordinary shoe, and frequently not require stabilization.

REFERENCE
Compere E L (1936) *J. Bone Jt Surg.* **18**, 692

Mr W V Anderson (*Edinburgh*) said that in deciding on the method of correction of leg inequality the various procedures had to be considered in each case; these were leg lengthening or shortening, and temporary or permanent cessation of growth, the correct choice of method of equalization being at least as important as the technique.

He preferred tibial to femoral lengthening because he believed that mechanical distraction of the femur must result in considerable forces being passed through the main joints of the lower limb, i.e. the hip and knee. Where the hip was already fused, as in tuberculous disease, with premature fusion of the knee epiphyses, the whole force was passed through the knee which was already deformed and distorted.

The first operation of tibial lengthening at the Princess Margaret Rose Hospital, Edinburgh, had been carried out by the late Mr W A Cochrane in 1932. Since then over 200 patients had been operated on.

Since 1949 a two-stage technique had been carried out. At the first the fibula was divided at its lower third and the proximal end of the distal third embedded in the lateral surface of the tibia. By this means development of a marked valgus deformity at the ankle was prevented. The second stage, the tibial osteotomy, was carried out when the tibio-fibular bridge had consolidated.

Since 1954 he had been using a simpler technique than open osteotomy of the tibia. In this the tibia was weakened by multiple drilling through one puncture wound and broken manually.

The distraction was carried out in the same way as before, using a modified Abbott machine incorporating tilting pin blocks and discarding the compression springs. This recent method did away with the long and rather ugly incision necessitated by the original operation. It also reduced the technique to one which was easy for the surgeon and surprisingly so for the patient.

Mr Denys Wainwright (*Stoke-on-Trent*) reported a series of cases of gross shortening of the leg associated with premature fusion of the epiphyses around the knee-joint following disease of the hip-joint. These cases were all associated with either short fibrous or bony ankylosis of the hip-joint with some flexion adduction deformity. The deformity had been corrected and from two to three inches of lengthening had been obtained by a sub-trochanteric oblique femoral osteotomy. After the operation the limb was immobilized on a sliding Thomas' splint, and lengthening obtained gradually by weight traction over a pulley, counter-extension being applied by the body weight with the end of the bed elevated. Many of these patients had been able to dispense with a raised boot and it was interesting to note that in a proportion of the cases in which a fibrous ankylosis of the hip-joint was originally present bony fusion had followed the osteotomy.

Section of Surgery

President Lambert C Rogers CBE VRD FRCS

Meeting March 1 1961

Treatment of Thyrotoxicosis

Dr W R Trotter (*London*)

Nonsurgical Treatment of Thyrotoxicosis

Subtotal thyroidectomy is a highly efficient method of treating patients with thyrotoxicosis. It does, however, involve admission to hospital and the inevitable unpleasantness associated with a major operation. The alternative nonsurgical methods of treating this disease therefore need to be considered in every case. These nonsurgical methods, antithyroid drugs and radioiodine, are at present less efficient in the sense that the proportion of patients rendered permanently euthyroid is smaller than after subtotal thyroidectomy. The purpose of this paper is to consider the reasons for this relative inefficiency, and how improvement might be achieved.

Antithyroid Drugs

Thyrotoxicosis is a disease with a very variable course. Bouts of thyroid activity may last from a few months to the greater part of a life-time. Hence the results of treatment cannot be adequately assessed without a long follow up. The two nonsurgical methods have only been in common use for ten to fifteen years, and hence little is known about their long-term effects. For this reason even a small series of patients with thyrotoxicosis treated prior to 1950 with antithyroid drugs alone may be worth considering.

The results obtained in 196 such patients are shown in Table 1. Nearly all had diffuse goitres, but there was no other conscious selection of cases. The intention was to see what proportion of patients could be successfully treated with antithyroid drugs alone. The series does not include cases deliberately prepared for thyroidectomy with antithyroid drugs, nor those whose treatment was interrupted after less than three months because of drug reactions or for other reasons. The antithyroid drugs used were thiourea, thiouracil and methylthiouracil.

Two patients treated with thiouracil died of agranulocytosis, at a time when antibiotics were not available to the civilian population.

Eleven patients died subsequently. The causes of death were not relevant to the thyroid condition or its treatment. Search is being made for the 22 patients who are still untraced. The present condition of 157 patients is now known. In 44% of these, treatment with antithyroid drugs had been abandoned in favour of thyroidectomy or radioiodine therapy. The precise reason for the failure of antithyroid drugs cannot be specified in all cases. Social factors were often important. The two main medical reasons were (1) the presence of a large goitre which the drugs could not remove and indeed sometimes exaggerated, or (2) the mere prolongation of treatment over a number of years. 10% of the 157 patients are at present taking antithyroid drugs. Most of these had gone through a period of remission, lasting several years, and subsequently relapsed. The 2 patients recorded as being thyrotoxic at the present time have high radioiodine uptakes, but are at full work and symptom free.

Deduction of the manifest failures leaves 70 patients (45%) who began their treatment before 1950, and are euthyroid at the present time. Only 56 of these, however, have been without any treatment for ten years or more, and can therefore be considered to be in a reasonably stable state. They cannot be described as 'cured', since recurrence of thyrotoxicosis is sometimes seen twenty to forty years after a subtotal thyroidectomy. The 56 patients who had achieved an apparently stable remission had required an

Table 1

Present state of 196 patients with thyrotoxicosis, who had been treated with antithyroid drugs before 1950

	No. of patients		
Dead	11		
Not yet traced	22	39	
Emigrated	6		
Thyroidectomy	28 (18%)		
Radioiodine	41 (26%)		
On antithyroid drugs	16 (10%)		157 (100%)
Still hyperthyroid	2 (1%)		
Euthyroid, no treatment	70 (45%)		

average of fifteen months' treatment with antithyroid drugs. The duration of treatment, however, varied from four to forty-five months. A course of treatment lasting more than two years cannot be regarded as altogether satisfactory, and a further 7 patients were eliminated on these grounds. This leaves a final group of 49 patients (31%), whose thyrotoxicosis was simply and satisfactorily treated with a course of antithyroid drugs of less than two years' duration, and who had remained well without further treatment for at least ten years.

That only about a third of an unselected group of patients with thyrotoxicosis fulfilled these criteria shows that in a quantitative sense this method of treatment is inefficient. Yet for those patients who have done well it has proved very satisfactory, since it did not involve hospital admission or interruption of the patient's normal activities other than 6 to 8 visits to the outpatient department yearly. In using this method of treatment we are dependent on factors in the patient himself, which we cannot at present define or modify, and which determine the natural course of his thyrotoxicosis. Our present efforts are directed at learning more of these factors. If it becomes possible to define the type of patient who will do well with this method of therapy, treatment with antithyroid drugs will certainly be the best we can offer to this particular group. In addition to its simplicity it has, with the more recently introduced drugs, the advantage of being virtually free of complications, and the particular merit of never causing permanent myxœdema.

Radioiodine Therapy

Experience with the use of radioiodine (^{131}I) for the treatment of thyrotoxicosis now extends over more than ten years, and has enabled us to define some of the problems. The most urgent of these is the control of dosage. The objective of treatment is the destruction of the greater part of the patient's thyroid by internal irradiation. It is an imitation, by non-operative means, of what the surgeon does when he cuts out the greater part of the gland. One fundamental difficulty in setting about this task, is that no rational explanation is available of the high success-rate of subtotal thyroidectomy. The surgeon can define the mass of tissue he leaves behind in the neck, but he knows nothing of its functional state, nor of its blood supply which must always be in some degree impaired. It is therefore remarkable that he is able, in nearly all cases, to leave behind a remnant of thyroid which is just about adequate (but no more) for the patient's physiological requirements; and perhaps even more remarkable that this remnant remains indefinitely at a more or less constant functional level without enlarging in response to the stimulus to the thyroid which must persist in many cases for years. It seems likely that the surgeon does something more subtle in performing a subtotal thyroidectomy than merely remove a lump of thyroid tissue.

The amount of radiation delivered to the thyroid, and therefore the amount of destruction to be expected, can be calculated in the individual patient with what might be considered sufficient accuracy for the purpose. The main uncertainty derives from the estimate of thyroid weight. Most of those who have worked on the subject are agreed that a desirable dose for the majority of patients lies in the region of 8,000 to 9,000 rads. However, two major unknowns concern (1) the distribution of radioactive material within the thyroid, which may be extremely irregular, and (2) variations in the radiosensitivity of individual thyroids. The magnitude of this last factor is not known, but it is almost certainly large. These two unknowns between them probably account for the fact that few people have been able to render more than 50% of thyrotoxic patients euthyroid after a single therapeutic dose of radioiodine. The remainder either develop myxœdema, or require one or more subsequent doses of radioiodine.

The problem of adjusting the dose of radioiodine to the needs of individual patients is a technical one which should certainly be capable of solution. Further experience of the long-term effects of radioiodine therapy is, however, demonstrating that another problem will also have to be faced which may well prove to be more intractable, that is delayed hypothyroidism. In our own series 42 patients have developed hypothyroidism, and in 14 of them (i.e. one-third) the condition did not appear until two to nine years after the last dose of radioiodine. Since few patients have been observed beyond nine years we cannot yet assess the incidence of delayed hypothyroidism. In our own series of 151 patients with thyrotoxicosis treated with radioiodine, the overall incidence of hypothyroidism was 17% at the end of the first year, but of 21 patients followed for nine years, 7 are now hypothyroid. The true incidence may be less than is indicated by these figures, since the follow up is incomplete, and the defaulting patients so far recalled have all proved to be euthyroid.

We have as yet no information about the causation of delayed hypothyroidism. Since it has always been preceded by a long period of euthyroidism this type of hypothyroidism cannot be directly related to the dose of radiation. A reasonable speculation would be that it is generated by some sort of immunological reaction. Delayed hypothyroidism is occasionally seen long after a subtotal thyroidectomy but is apparently less common than after radioiodine treatment.

In summary, treatment with antithyroid drugs is the simplest and most satisfactory treatment for a proportion of patients with thyrotoxicosis. This proportion probably does not amount to more than about a third of the total, and we cannot as yet select these patients efficiently before treatment is begun.

Treatment with radioactive iodine gives many excellent results in the first two years after therapy, though more work is required on methods of assessment of dosage. The occurrence of delayed hypothyroidism suggests that the late results will be less good, and it is not yet easy to see any possible way of preventing this complication.

Table 1
Classification of New End series of goitres

Diffuse toxic		904	25·8%
Diffuse colloid (non-toxic)		146	4·2%
Nodular (toxic and non-toxic) (includes 3 mediastinal ectopic)		1,906	54·5%
Single nodules		321	9·2%
Lymphadenoid goitre		92	2·6%
Malignant:			
Carcinoma	105	113	3·2%
Sarcoma	8		
(includes one mediastinal ectopic)			
The remainder:		18	0·5%
Acute inflammatory	1		
Fibrous thyroiditis (one in ectopic nodule)	5		
Carcinoma œsophagus	1		
Carcinoma bronchus	1		
Subacute thyroiditis	6		
Tuberculous	2		
Eosinophilic granuloma	1		
Lingual	1		
		3,500	100%

Mr M J Lange (*London*)

Morbidity and Mortality in Thyroidectomy

My function in this discussion is to present figures from the New End Endocrine Unit to show the risks of thyroidectomy, and the frequency of complications. The thyrotoxic and the nontoxic cases are considered together for two reasons: (1) Because our operative technique is basically similar for the two types, only differing in the way the gland is sectioned. (2) All patients coming to surgery are clinically nontoxic. Those that initially were toxic are rendered nontoxic. Where relevant, differences between the two groups will be indicated.

Between the years 1947 and 1959, 3,500 thyroidectomies, partial, selective and total, were undertaken by one surgical team at the Endocrine Unit, New End Hospital (Table 1). Fig 1 shows the age distribution, in five-year periods, of these patients. Four patients were under 9 years of age, the youngest, a little girl of 4, presenting with typical exophthalmic thyrotoxicosis. She was detoxicated with Neo-Mercazole, prepared with iodine, and then underwent thyroidectomy. Four years later she is perfectly well, of correct height and weight for her age, and doing well at school. 104 patients were over 70 years of age, 35 over 75 and 7 were over 80. We see therefore that age is no contraindication to surgery.

Pressure symptoms were complained of in just under half (48·9%) and obvious stridor was present in 3·4%. Half (49·9%) were clinically toxic. Of these, three-quarters needed preparation for surgery with one of the antithyroid drugs, Lugol's iodine sufficing for the remainder. Among the last 964 toxic patients analysed, there were 171 (17·6%) who had previous courses of the antithyroid drugs, in the hope of gaining permanent remission, but had relapsed.

Of the 3,112 female patients (88·9%) in the relevant age groups, there were 49 pregnant patients. Pregnancy is not regarded as a contraindication to thyroidectomy but we prefer to operate between the third and sixth months. Two-thirds of the 49 were toxic, half of them needing preparation for surgery with antithyroid drugs and the other half requiring Lugol's iodine only. In these pregnant patients, if the toxicity has not been brought under control by the sixth month then surgery is postponed. The antithyroid drugs are continued until the toxicity does come under control and the dosage then reduced to a main-

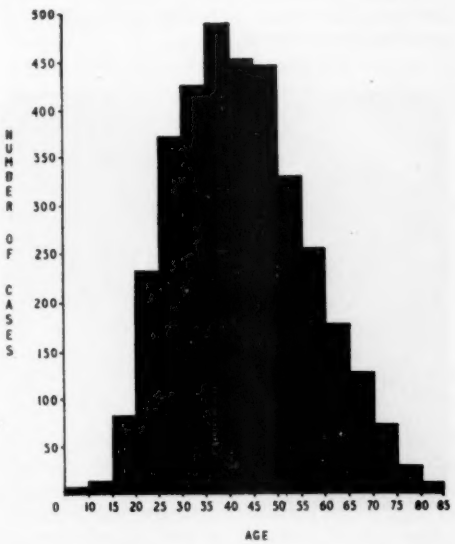

Fig 1 *Age distribution of patients*

tenance level. This is then continued to, or beyond parturition, though a number of these patients appear to remit as term approaches. Following parturition each patient can then be reviewed for definitive treatment.

The strap muscles were sectioned in 9·6%, being sectioned bilaterally in one-fifth of this number. Approximately half needed drainage. 16% had retrosternal prolongations. Posterior mediastinal goitres, contrary to general belief, are not uncommon, occurring in 3·4% of the last 2,500 patients analysed. A deeply placed goitre, with perhaps pressure symptoms, that moves poorly on swallowing and in which the X-ray reveals an anteriorly displaced trachea should be suspect (Fig 2).

The sternum was split on 7 occasions, in 4 for true intrathoracic ectopic goitres, one of which was carcinomatous. These goitres derive their blood supply from within the mediastinum and it would be hazardous to attempt delivery from the neck. Of the remainder, 2 were cervical goitres with retrosternal projections and one an advanced malignant goitre. One hundred and seventy-six patients (5%) had had previous operations on their goitres, but of this number only 21 had had their initial operation at New End, giving a recurrence rate for the unit of 0·6%.

There was a danger of carcinoma of the thyroid developing as a result of antithyroid drug treatment. In 2 patients in the series who had been treated with Neo-Mercazole histological examination following thyroidectomy revealed carcinomatous change.

Fig 2 *Forward displacement of trachea as a result of a posterior mediastinal goitre. Calcification is present*

Table 2
Complications

Serum collection		9·7%
Transient tetany		1·7%
(no case of permanent tetany)		
Recurrent laryngeal nerve damage		1·9%
(50% recovery)		
Sepsis		1·5%
Keloid (or anticipated) scars		3·8%
Hypothyroidism		9·2%
(including lymphadenoid goitres)		
Other:		1·4%
Pulmonary	18	
Pneumothorax	2	
Air embolism (recovery)	2	
Coronary thrombosis	1	
Peripheral thrombosis	2	
Tracheostomy	1	
Nickel sensitivity	5	
Horner's syndrome	3	
Retention of urine	1	
Evacuation of clot	13	
No tracheal collapse		
No crisis		

Complications (Table 2)
Serum formation, clear or sanguineous, occurred in 9·7%. To a large degree this is probably attributable to the use of catgut, which we use exclusively except for the ligation of the inferior thyroid artery. This complication usually appears on the fifth or sixth day, and the serum is best evacuated by inserting the blunt end of a sterile needle at one end of the scar. Repeated evacuation may be necessary and may prolong the patient's stay in hospital for a day or two.

Transient tetany occurred in 1·7%. There were no cases of permanent tetany in non-malignant goitre. This complication occurred more frequently in the toxic goitre in the ratio of 3 : 2. Recurrent laryngeal nerve damage occurred in 1·9%, half of whom showed recovery within a few months. In those cases where paresis was only temporary, it occurred three times more commonly in the toxic patient, whilst where the damage was permanent, it was three times commoner in the nontoxic. We do not make it a routine to expose the nerve at operation, but we are on the look out for it. We inspect the area where it should be, the area where it might be, and finally before sectioning the lobe we make quite certain that it is nowhere near the intended line of section. We frequently do see the nerve, but not as a result of deliberate dissection except in total thyroidectomy.

Sepsis occurred in 1·5%. No case gave rise to anxiety. A small number of patients referred, perhaps 2 or 3 annually, had developed repeated sinus formation and discharge of non-absorbable sutures. Sepsis occurred with equal frequency in the toxic and the nontoxic.

Although the figure of 3·8% for keloid scar formation may appear high, it includes anticipated keloid formers. Patients in whom the scars appear unduly pink and raised a few days after

operation, and who complain of local tenderness and a 'prickly' sensation, are referred for surface irradiation. The results are uniformly good. In established cases of keloid scars, excision of the scar is carried out combined with pre- and/or post-excision irradiation.

The figure of 9·2% developing hypothyroidism is reduced to 6·6% if the lymphadenoid goitres are excluded. The latter figure of 6·6% includes many goitres that on microscopical examination reveal lymphadenoid infiltration – a feature that often heralds hypothyroidism. Hypothyroidism occurred with equal frequency in toxic and nontoxic patients.

The pulmonary complications (atelectasis, pneumonia, &c.) and the two cases of pneumothorax all responded to routine measures.

Both cases of air embolism occurred under similar circumstances – the neck being in extension and one of the tightly stretched anterior jugular veins being accidentally incised. The first warning was a hissing noise as air was drawn into the open vessel. A finger was promptly applied to the site of injury and the central portion of the affected vein was clamped. The hissing noise was followed within seconds by the most frightening machinery-type cardiac murmur which was audible throughout the operating theatre. Fortunately, both patients, middle-aged females, recovered completely. One complained of post-operative headaches for a few days whilst the second appeared a little tardy in coming out of the anæsthetic.

The 3 cases of thrombosis responded well to anticoagulant therapy.

The patient requiring tracheostomy was a feeble woman of 79 who had a 560 g goitre removed. The day following operation she was too weak to expectorate copious purulent sputum. A tracheostomy brought prompt relief and was followed by full recovery.

The nickel sensitivity followed the use of metal clips. Local soothing applications quickly brought relief. The probable cause of Horner's syndrome, which occurred in 3 patients, is the dissection of a low and laterally placed inferior thyroid artery.

In those patients needing evacuation of clot from the wound, there was only one really urgent case – a middle-aged man who quickly developed stridor and whose wound had to be ripped open in the ward to prevent asphyxia. The remaining 12 were taken back to theatre, the clot evacuated and the wound re-sutured. This occurred with equal frequency in nontoxic and toxic goitres.

There were no cases of post-operative tracheal collapse in this series, and it is my impression that when this rare complication does occur, it is usually associated with nerve damage.

No case of thyroid crisis was encountered and this is almost certainly due to the fact that toxic patients are not operated on until adequately controlled with antithyroid drugs.

The overall average post-operative stay in hospital for the first 1,000 cases was twelve days. At present, in an uncomplicated thyroidectomy for a toxic or nontoxic goitre, the average post-operative stay is seven to ten days.

In this series of 3,500 thyroidectomies there were 20 deaths. Of the 10 deaths in non-malignant goitre, half occurred in toxic patients, brief details of whom are as follows:

Case 1 Female, 74. Died one month after operation with cerebral thrombosis.

Case 2 Female, 59. Severely ill with thyrotoxicosis and congestive cardiac failure. In spite of all measures continued to deteriorate. Staged operations decided on. Superior thyroid vessels ligated under local anæsthesia. Died forty-eight hours later in cardiac failure.

Case 3 Female, 36. Recurrent toxic goitre with long history of asthma. We misjudged her reserve and she died on the fifth post-operative day.

Case 4 Female, 65. Died on the third post-operative day in congestive cardiac failure.

Case 5 Male, 58. In addition to the thyrotoxicosis had pulmonary tuberculosis and myocardial degeneration. Died within a few hours of removal of a goitre weighing over 400 g.

We consider the follow-up clinic an integral part of the unit and like to see every patient who has been operated on at least once after discharge from hospital. The development of post-operative hypothyroidism is not serious, provided it is recognized and treated. Failure to do so may result in months, and even years, of ill health and in bringing the operation of thyroidectomy into disrepute. In this series over 95% were seen in the follow-up clinic one month after the operation, 80% were followed up for three months, 66% for six months and over 44% were seen for a year or longer.

In conclusion, it is submitted that we are justified in recommending surgery for the large majority of goitres, toxic or nontoxic, requiring treatment.

Mr J E Piercy (*London*)

Factors Contributing to Safety in Surgery of the Thyroid

Surgery of the thyroid with its present low rate of mortality and morbidity has been made possible largely by the researches of physicians, biochemists and physicists, resulting in methods of thyroid detoxication and control. At the beginning of the century, of 100 cases operated on in London hospitals by unilateral extirpation, 23

died during or immediately after operation. At present, with the majority of toxic goitres brought to a nontoxic state by means of the antithyroid drugs, surgeons with an interest and experience in thyroid surgery can show a low mortality, particularly if they have radioactive iodine available for treatment of thyrocardiac cases with congestive failure. Before the days of the antithyroid drugs, the margin of safety was small and many of the highly toxic cases underwent operation by stages, the superior vessels being ligated in one or two stages, and the lobes being removed one at a time still later. 'Stealing the goitre', too, was occasionally resorted to.

As an example, the operation list at New End Hospital one day in 1934 included the following 3 patients. One had a retrosternal prolongation, auricular fibrillation, laboured breathing from cardiac failure and tracheal pressure, and fluid in the pleural cavity. Removal was performed in stages. The second, a case of severe primary toxic goitre, had a resting pulse of 120, which rose after Avertin to 200. Operation was postponed and the bowel washed out. Later, the superior vessels were ligated under local anæsthesia, and still later, one lobe at a time was removed. The third case had been confined to bed for several months awaiting an optimum time for operation, during which the pulse had rarely fallen below 120. Such cases were not conducive to a low mortality.

Ten years ago, the mortality in 1,000 partial thyroidectomies, excluding those from malignant disease, was 0·6%, death being due to cardiac failure in 3 congestive cases with auricular fibrillation, to pulmonary emboli in 2, and to congestive failure in 1, having been hurried on by a postoperative hæmorrhage (no toxic crises). This greatly reduced mortality was due to the preparation for operation by antithyroid drugs and the fact that patients were sent to hospital during the early stages of toxicity.

In a recent series, we find 1 death in 1,400 operations, as compared with 6 in 1,000 operations ten years ago, the improvement being partly due to selection, as we now refer thyrocardiac cases with a low cardiac reserve and possibly congestive failure to our Isotope Department for radioactive iodine therapy. This has eliminated deaths due to cardiac failure, the one death being due to pulmonary embolism the morning after operation. Bringing all primary toxic patients and those with nodular goitres of over-average toxicity to a euthyroid state by means of carbimazole has eliminated thyrotoxic crises and the many other previous anxieties.

Pseudo-crises are occasionally met, and arise in a patient who has been brought to a euthyroid state, but whose operation has been postponed and undertaken later, when control has been partially lost. The post-operation picture is that of restlessness, panic, and a very rapid pulse, but without the typical sweating. It has never led to death, but has taught us always to continue the maintenance dose of Neo-Mercazole until a day or so before the patient's admission.

The recurrent laryngeal nerves are not identified as a routine when they are in their normal anatomical position. A search is made for the nerve at every stage of the operation after ligation and section of the middle thyroid veins, in case it has been displaced forwards, either in front of, or by adhesions to, the capsule of an adenoma. Then only is it identified and dissected free. It is also exposed during a total thyroidectomy; and during a subtotal when there are multiple nodules in the posterior margin of a lobe. Further safeguards include the exposure and ligation of the inferior thyroid artery as it emerges from under the carotid; isolation, ligation and section of the inferior thyroid veins at an early stage and under direct vision; and dislocation of the upper pole with the superior leash of vessels, which is made possible by stripping the fascia off its posterior wedge. Further factors are the oblique method of sectioning the lobe without the use of marker forceps and hæmostasis. Gentleness must be used in dislocating a retrosternal projection, particularly from the posterior mediastinum.

The recurrent goitre rate is a fraction of 1%, the low incidence being due to removal of all nodular tissue and ligation of the inferior thyroid arteries in nearly all patients. In the recurrent cases operated on, there is invariably a large inferior artery on the side of the re-growth. The remnants of tissue are flat, the capsule being sutured to the tracheal fascia, leaving little raw surface or unencapsulated tissue visible.

The operation for the nodular goitre is a selective procedure, with no visible nodules remaining. Remnants are reconstituted from compressed capsular tissue and from other tissue considered normal such as an upper pole. The inferior thyroid arteries are ligated. The pyramidal lobe is completely removed and when dealing with what is apparently a discrete adenoma, the opposite or normal side is nevertheless explored and its anterior surface removed.

There has been no incidence of permanent tetany. Transient tetany is not infrequent (1·7%) being quickly controlled, however, by calcium lactate, gr 75 t.d.s., continued for six to seven days.

Care is taken to identify and preserve all parathyroid glandules. They are frequently located in the fascia near the inferior thyroid veins. This fascia is carefully preserved, even though the parathyroids are not identified. They are also found attached to the inferior wedge of the upper

pole or in relation to the inferior thyroid arteries. The glandules are often camouflaged by a surround of fat, and a method for their identification is to pinch with forceps and slightly traumatize a suspected portion of tissue, which will quickly form a hæmatoma if parathyroid, and become blue or blue-black in colour.

An X-ray taken of a retrosternal goitre may suggest that its removal will be a formidable procedure. This is rarely the case, however, if the large veins binding it down are identified, doubly ligated and sectioned before delivery. If, however, the mass is solid and impacted, or if its capsule is adherent to the mediastinal tissues, or the mass is truly intrathoracic in type and with no connexion with a cervical thyroid, the sternum must be sectioned to allow for its delivery. Any surgeon undertaking the surgery of that endocrine triad, the thyroid, parathyroid and thymus, must be prepared to extend his range, when called upon, deep into the mediastinum.

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The Recurrent Laryngeal Nerve

Injury to the recurrent nerves is a well-recognized hazard of thyroidectomy, and is particularly liable to occur in operations for toxic goitre. While transient nerve injuries after operation rarely cause concern even when bilateral, permanent injury to the nerve can be a serious complication. In view of the danger of recurrent nerve injury at thyroidectomy, it is surprising that there is such a difference of opinion in surgical circles as to the best method of protecting the nerves. It is obviously a sound surgical principle to identify and expose an important structure in the operative field which is liable to injury, yet this principle is disregarded at thyroidectomy by many experienced surgeons because they believe that the recurrent nerve is particularly susceptible to trauma, and is more liable to damage if looked for than if left undisturbed. Other surgeons accept Lahey's view (1938) that the nerve is no different from other peripheral nerves and should be identified routinely at operation. I practise identification of the nerves at thyroidectomy because I consider that the nerve is less liable to permanent nerve damage, as opposed to transient damage, if it has been exposed at operation. I suggest that a study of the injury rate for nerves at thyroidectomy supports this view.

Injury Rate

In general surgical practice, the injury rate in experienced hands, for a mixed series of primary operations on simple and toxic goitres, whether the nerve is identified or not, is in the neighbourhood of 2 to 4% of nerves at risk (Blackburn & Salmon 1961, Gisselsson 1949, Hawe & Lothian 1960, Riddell 1956, Till 1955, Wade 1960). In a special clinic the rate may be smaller, but in inexperienced hands it may be much higher.

The injury rate in itself is not so very important. What is important is the percentage of injured nerves which are permanently damaged as opposed to those that recover. In the series of thyroidectomies without nerve identification published by Till (1955) and by Gisselsson (1949) this figure averaged 32%; that is to say one injured nerve in three was permanently damaged. On the other hand, in Hawe & Lothian's series (1960), of over 1,000 thyroidectomies in which the nerves were identified routinely, only one injured nerve in 9 was permanently damaged, and in a series of thyroidectomies with nerve identification which I studied recently (Wade 1960), 6 out of 215 nerves at risk were injured – an injury rate of 2·8% – but there was no permanent cord paralysis. In the past year my injury rate rose to 4% but again all the nerves recovered completely.

My conclusion is that in experienced hands the injury rate is probably very similar whether the nerve is identified or not. I am, however, convinced that permanent injury is more frequent if the nerve has not been identified. If the nerve has been identified at operation it is most unusual in my experience for full function of the cords not to return after injury, usually within a few weeks if the cord paralysis has been partial, and within two or three months if the cord paralysis has been complete.

Other Factors

There are factors other than the risk of permanent cord paralysis which might influence a surgeon's views on the advisability of exposing the recurrent nerves at thyroidectomy.

(*a*) *The risk of injury to parathyroid glands:* It would seem that much of the damage done to the parathyroids at operation is due, not to accidental removal, but to infarction of the gland through thrombosis of its end artery. There is, therefore, a possibility that nerve identification, with of necessity an increased amount of dissection and ligation of blood vessels in the neighbourhood of the parathyroid glands, may increase post-operative parathyroid deficiency.

At the moment there is no proof of this. In the series of 119 thyroidectomies which I studied, the incidence of post-operative hypoparathyroidism was 4·5%, which is not significantly greater than the expected incidence of 3%. Furthermore, Davis *et al.* (1961) recently carried out a survey in practices in and around Cardiff to assess the amount of unsuspected parathyroid insufficiency

after thyroidectomy. Using the calcium deprivation test they found borderline hypoparathyroidism in a surprisingly large number of patients, but I am assured that the cases were about equally divided between surgeons who identified the nerve and those who did not.

My view at present is, therefore, that nerve identification does not increase the risk of parathyroid damage.

(*b*) *The frequency of extralaryngeal branches of the nerve:* It has been suggested that the frequency of extralaryngeal branching of the recurrent nerve makes nerve identification in the thyroid area difficult and dangerous. Two or more extralaryngeal branches are certainly not uncommon, but my experience at operation has been similar to that of Hawe & Lothian (1960). The branches usually remain close to each other and are seldom separated by branches of the inferior thyroid artery, so that exposure rarely presents any difficulty.

(*c*) *The risk of delayed nerve paralysis:* It has been suggested that delayed paralysis is liable to follow identification of the nerve at operation, on account of organization of blood and exudate around the exposed nerve. I am sure that reactionary œdema can cause the onset of a transient paralysis some hours after operation, but I have been unable to find any authentic case of permanent nerve paralysis, following nerve identification, delayed for more than a few hours after operation. In the series of thyroidectomies which I studied and in which 215 nerves were at risk, all patients were re-examined one to three and a half years after operation. In no case did cord paralysis develop in the period between the immediate post-operative laryngoscopy and the final examination. I consider that there is no evidence to support the view that nerve identification predisposes to delayed paralysis.

Operative Technique

While the nerve can be handled with impunity in most cases, it should never be handled unnecessarily, as this increases the chances of subsequent transient paralysis. However, it must be exposed sufficiently to ensure, by sight, that it is not damaged during resection of thyroid tissue or whilst securing hæmostasis. The following points in the operative technique are important:

(1) *Adequate exposure of the operative field:* In order to expose the important postero-medial surface of the thyroid gland and the superior thyroid pedicle, the sternomastoid muscles should be mobilized by incising the deep fascia along their medial borders, and the pretracheal muscles should be cut transversely on both sides.

(2) *Division of the inferior thyroid veins:* The inferior thyroid veins should not be ligated and divided until the nerve has been identified. The nerve often runs dangerously close to these veins and can easily be caught up in a ligature.

(3) *Ligation of the inferior thyroid artery:* After mobilizing the thyroid lobe the trunk of the inferior thyroid artery should be ligated in order to secure as bloodless a field as possible when searching for the recurrent nerve.

(4) *Identification of the recurrent nerve:* The nerve should first be sought in the lower third of the operative field as it passes obliquely across the œsophago-tracheal groove. The nerve is then traced upwards and extralaryngeal branches can be identified as they arise.

(5) *Freeing the nerve from the goitre:* It may be necessary to ligate and divide branches of the inferior thyroid artery and to incise fascia, in order to free the nerve from the goitre and displace it away from the proposed line of resection.

(6) *Mobilization of the superior pole of the thyroid:* The superior thyroid vessels should be exposed as a pedicle and divided between ligatures. This can only be done with ease and certainty if the pretracheal muscles have been divided and turned back. This manœuvre enables one to displace the superior pole of the thyroid medially, and to expose the nerve as it enters the larynx.

(7) *Anomalous recurrent laryngeal nerve:* If the right recurrent nerve cannot be found in its usual course an anomalous nerve should be suspected. An anomalous nerve is present in 1% of cases; it usually loops forwards and medially above the trunk of the inferior thyroid artery, and then takes the same course as does the normal recurrent nerve in the last $\frac{3}{4}$ in. of its extralaryngeal course.

Conclusion

Injury to the recurrent laryngeal nerve is an unavoidable risk of thyroidectomy, particularly in operations for toxic goitre. I believe in identifying the nerves at operation, because I am convinced that the risk of permanent injury to the nerves is thereby diminished. I should be prepared to change my mind only if I felt that the dissection necessary to identify the nerves was responsible for an unacceptable rate of post-operative parathyroid insufficiency. At present there is no evidence that this is so.

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Section of Odontology

President R V Bradlaw CBE FRCS FDS RCS

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Paper

The Neurohistology of Human Dentine

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John Hunter (1770), writing about the sensitivity of the teeth, observed that this sensitivity is due to the nerve in the cavity of a tooth and his account reads: 'We do not observe the same violent effect from any other nerve in the body being exposed either by wound or sore, as we do from the exposure of the nerve of a tooth. Perhaps the reason for the intenseness, as well as the quickness of the sense of heat and cold in the teeth, may be owing to their communicating these to the nerve sooner than any other part of the body.'

It is not surprising, therefore, that the point of greatest controversy since Hunter's comments has been whether sensory nerves end at the periphery of the pulp or whether they end in the calcified part of the dentine.

None of the research workers who have since attempted to demonstrate nerves in this tissue can be said to have done so unequivocally. The literature, which has been reviewed by Brashear (1937), Bernick (1948) and Arwill (1958), remains inconclusive.

One of the most important objectives in the interpretation of histological data is to attempt to relate histological appearances with the living state. Almost invariably the early research which has stood the test of time is that of such workers as Retzius, Schwann, Tomes, Boll and many others who, in spite of great technical difficulties and, by modern standards, crude instruments, gave us vivid and accurate factual descriptions of the tissues which they studied, although their interpretation was often in error. It is significant that these workers examined freshly obtained tissues which were often unfixed and they applied only the simplest of chemical and physical tests to them. It is the evolution of the complicated series of manipulations now commonly employed in modern histology and which purport to show structures more clearly, that has given rise to complex artifacts which are extremely difficult to interpret and which tend to obscure an understanding of cytology as a vital process. In fact there are cases where failure to appreciate the distinction between the living state and the appearance of fixed sections has led to a retardation rather than an advance of knowledge. The innervation of human dentine is a problem which should be viewed in this light.

My approach to the problem of the neurohistology of dentine was, therefore, to study first the nerve fibres in vertebrate skin in the fresh unfixed and unstained state and then after staining with methylene blue, using the techniques of Schabadasch (1935). The results were then compared with those obtained from sectioned material after various fixative, embedding, decalcification and metallic impregnation procedures. The morphology of the nerves demonstrated by these techniques was compared carefully with that shown by other workers, namely Weddell & Zander (1950), Harrison (1907, 1910), Speidel (1932, 1933, 1935, 1942) and Hughes (1953). Many of the simpler experiments of these workers were repeated in order to gain experience of the appearance of the morphology of nerve fibre terminations under various conditions. For example, growing nerves were watched for short periods in the tails of living amphibian larvæ and post-mortem changes were followed in methylene-blue preparations of terminal nerve fibres in mammalian skin.

In the naked terminal portion of nerves, marked changes in the outline of the axon are frequently present in the form of minute bead-like swellings. Fusiform and vesicular enlargements also occur in this part of the nerve and these are often associated with changes in the staining density of the axoplasm. The full significance of these changes in the outline form and the changes in staining density of the axon is by no means established. It is quite possible that beading, swelling and vesiculation of axoplasm are post-mortem changes or are produced by treatment with fixatives. This is

not a completely satisfactory explanation, however, since according to Speidel (1935, 1942) many of these structural features can be observed in living nerves. The small spherical, densely staining beads are often, but not invariably, arranged regularly along the axon near its termination. The diameter of axons possessing such beading is usually below 1μ and there is no supporting Schwann cell. Less frequently, small spherical enlargements with unstained centres containing vacuoles can be found in the axon; these I call vesicular swellings to distinguish them from the spindle-shaped or fusiform swellings with unstained centres that also occur. Fusiform bodies with unstained centres are frequently formed at the junction of two or more branches. Occasionally, at what appears to be the growing tip of an axon, flattened film-like areas of lightly stained axoplasm, often containing droplets of stained material and vacuoles, may be found. These strongly resemble the growth cones of growing nerves. The bead-like, vesicular and fusiform structures, therefore, provide a valuable guide for the identification of small nerve fibres. These structural characteristics of small terminal axons are, furthermore, related to the state of the axoplasm at the time of fixation (Fig 3).

My own study of the neurohistology of human dentine has been made mostly on silver impregnated material. It is appropriate at this juncture, therefore, to outline the morphological characteristics of silver impregnated fibres which are regarded as nerve fibres in this study. Silver impregnated fibres not associated with Schwann cells were regarded as nerve fibres only if they satisfied the following six criteria:

(1) The diameter of the fibres should fall within the size range of terminal nerves, i.e. 1·0μ and less.

(2) The silver deposited in or on the fibres should possess a fine grain size resulting in an apparently smooth impregnation in obvious contrast to the coarse grained deposit of silver more commonly found in non-neural connective tissue fibres. This criterion is only valid for the silver technique finally adopted for this study, since the quality of the impregnation depends entirely on the care with which the various stages in the impregnation are controlled (Fearnhead & Linder 1956).

(3) The presence of densely impregnated beads, or lightly impregnated fusiform or vesicular swellings, situated periodically along the fibres, was regarded as an important morphological characteristic indicative of small terminal naked axons.

(4) The presence of branching, in fibres, which also satisfied conditions (1) to (3) was regarded as an additional feature consistent with the morphology of terminal nerve fibres.

(5) The criteria (1) to (4) were only regarded as valid if, in the same section, fibres of similar size and morphology could be found in continuity with larger nerves.

(6) That the fibres in the dentine and pulps of teeth which satisfy all the previous criteria, should disappear following nerve resection experiments.

Material and Methods

Both pre-natal and post-natal human teeth were studied. The pre-natal material consisted of the complete or partial dentitions of 13 fœtuses ranging from approximately 6 weeks to 7 months menstrual age. I am indebted to Professor J D Boyd for the loan of 5 of these specimens. These were the only preparations impregnated with silver by the De Castro method. The post-natal material consisted of 18 deciduous teeth with an age range of 3 days to 9 years, 29 permanent teeth obtained from patients between the ages of 10 years and 53 years, and 25 permanent teeth of unknown age. Some of the teeth studied were carious; some, extracted for orthodontic purposes, were apparently caries free. With the exception of the De Castro impregnated sections the fixatives used were either 10% neutral formol saline, or Bouin's fixative. Decalcification was achieved with formic acid/sodium formate solution according to the method of Kristensen (1948). The silver impregnation method used was that described by myself and Linder in 1956. A monkey was used for the experimental section of the nerve supply to the teeth.

Observations

Pioneer nerve fibres arrive very early in the embryonic tissues of the jaws and quite large nerve trunks are present and well established in the tissue in which the tooth germs develop and grow. According to Hogg (1941) intra-epithelial sensory nerves can be demonstrated and correlated with functional capability in human fœtuses of 8–14 weeks menstrual age, when the fœtus is approximately 30 mm crown-rump length.

The dentine papilla is small in this early stage of tooth development and nerve fibres can be demonstrated in close relationship to the tooth germ. In spite of their close proximity to the base of the dentine papilla, the nerve fibres are orientated tangentially to the tooth germ and do not enter the substance of the dentine papilla (Fig 1A). The bending of these fibres suggests that they had either deviated in their course to avoid the growing tooth germ or that the tooth germ had pushed its way between groups of fibres already present. In the light of current views each of these possibilities is reasonable since not only may the path of the growing nerve be deflected by the orientation

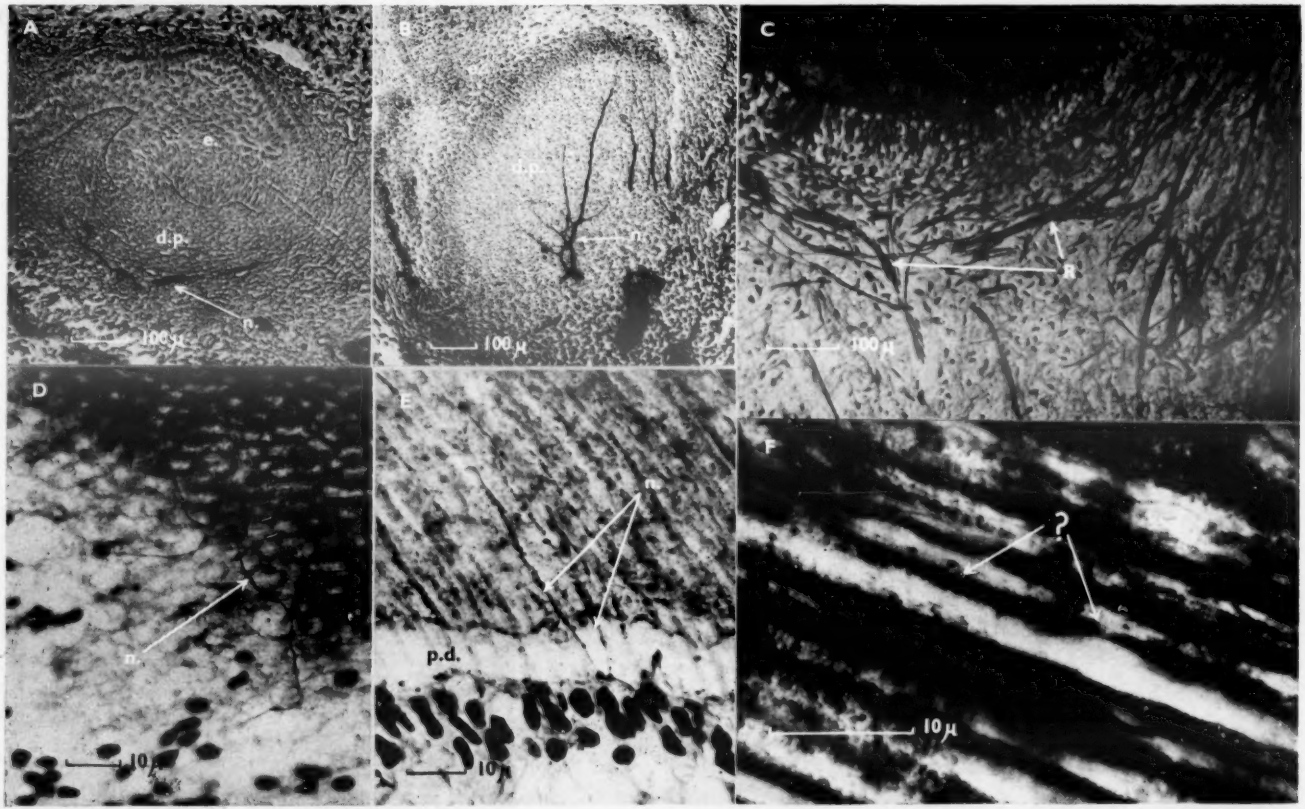
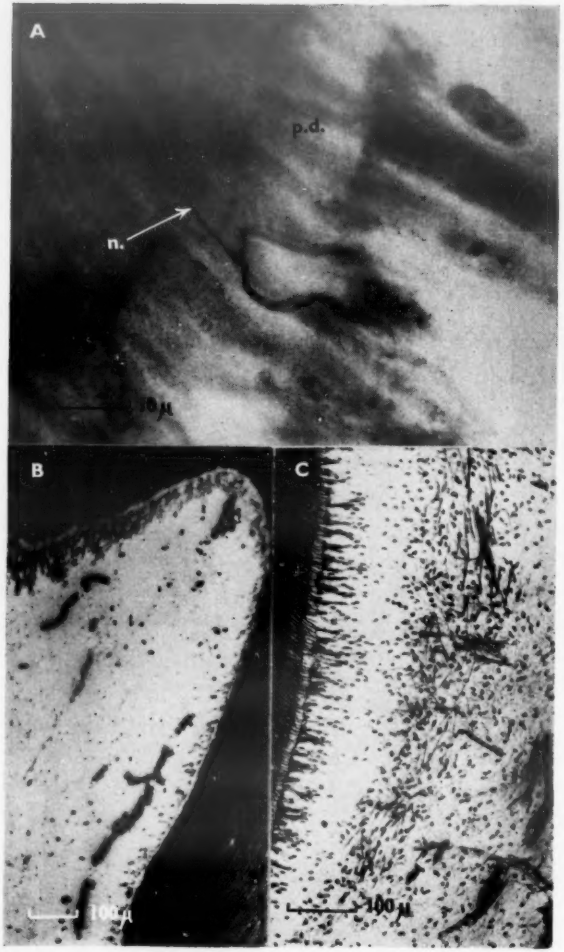


Fig 1A, *Longitudinal section through an incisor tooth germ of a male human fœtus 48 mm C.R. length. De Castro silver impregnation method.* **B**, *Longitudinal section through a canine tooth germ in the 'Bell stage' of tooth development in female human fœtus 68 mm C.R. length. De Castro silver impregnation method.* **C**, *Longitudinal section of a human lower molar tooth.* **D**, *Branching nerve fibres of the marginal plexus. Tangential section through the pulp-dentine junction of a human pre-molar tooth.* **E**, *Longitudinal section through crown of a human molar tooth showing beaded intratubular nerve fibres arising from a nerve fibre of the marginal plexus.* **F**, *Silver impregnated beaded fibre of uncertain identity in the outer third of the dentine.* **n**=*nerve fibres*, **e**=*enamel organ*, **d.p.**=*dentine papilla*, **d.t.**=*dentinal tubule*, **p.d.**=*predentine*, **R**.='*plexus of Raschkow*'. *Unless otherwise stated all sections were impregnated with silver by the method described by Fearnhead & Linder (1956)*



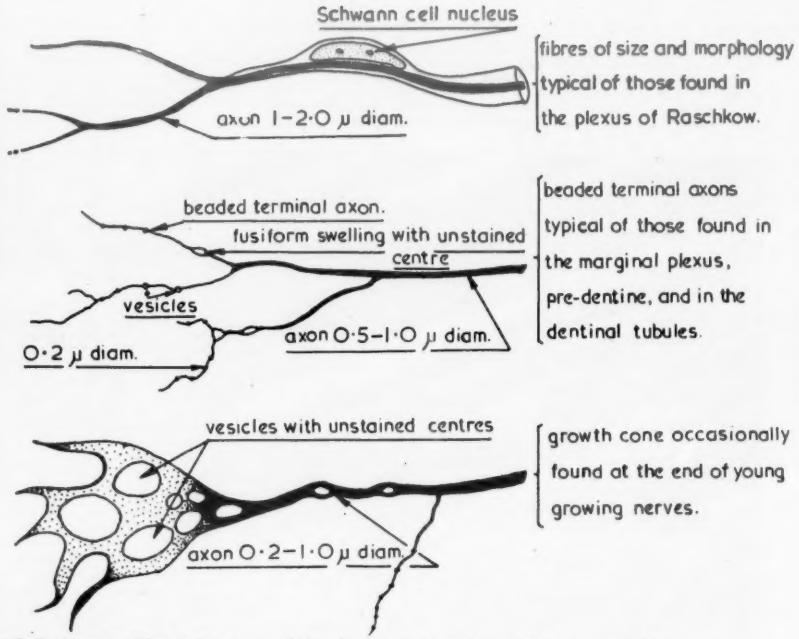

Schwann cell nucleus
axon 1-2·0 μ diam.
fibres of size and morphology typical of those found in the plexus of Raschkow.
beaded terminal axon.
fusiform swelling with unstained centre
vesicles
0·2 μ diam.
axon 0·5-1·0 μ diam.
beaded terminal axons typical of those found in the marginal plexus, pre-dentine, and in the dentinal tubules.
vesicles with unstained centres
axon 0·2-1·0 μ diam.
growth cone occasionally found at the end of young growing nerves.

Fig 3 *Diagram illustrating some of the characteristic features of nerve morphology commonly observed in this study*

←Fig 2 A, *An intratubular nerve fibre in the dentine of a lower molar tooth of a monkey* (Cercocebus fuliginosus). B, *Appearance of a longitudinal section of the pulp-dentine junction of the crown of a molar tooth of a monkey* (Cercopithecus sabæus) *one month after resection of the inferior dental nerve.* C, *A similar region showing the typical innervation of the normal pulp, for comparison with* B. n=*nerve fibres,* p.d.=*predentine.*

of the cell interfaces at the base of the developing tooth germ but angulation of the nerve fibres can be caused by growing organs pushing against them (Weiss 1955).

The first pioneer nerve fibres arrive in the dentine papilla during the late bell stage of tooth germ development and usually follow the course of the vessels (Fig 1B). By the time dentinogenesis commences most tooth germs possess one or more nerve fibres. These observations have also been recorded by Maccaferri (1956) and Madajan (1958). These pioneer nerve fibres have a diameter of approximately 1·0–2·0μ and less. During the period of development commencing with the onset of dentinogenesis and ending with the completion of the root, there is a marked increase in the number of nerve fibres of the pulp in both deciduous and permanent teeth, the diameter of the fibres remaining relatively small. In the permanent teeth with root formation nearing completion, the plexus of Raschkow was present in most cases, whereas this plexiform arrangement of nerves was not apparent in the deciduous teeth at a similar stage of development.

In deciduous teeth approximately twelve to sixteen months elapses from the commencement of dentinogenesis, at which time it may be assumed that the first pioneer nerve fibres are present, to the time when the root is completed. The corresponding period of development for permanent teeth is, however, much longer, namely six to nine years. This great difference in the time available for development has a particularly important bearing on the pattern of the innervation. It is quite clear that it is impossible to compare the pattern and density of the innervation of the deciduous and permanent teeth at morphologically similar developmental stages without taking this discrepancy in developmental timing into consideration.

In the young fully-formed tooth, varying numbers of nerve bundles, some containing few fibres and some containing many fibres of different sizes, enter the pulp canal through the apical foraminæ and the lateral canals. These nerves usually, but not invariably, accompany blood vessels; the majority are myelinated, a few only being nonmyelinated. Some of the nonmyelinated nerves can be followed for considerable distances and are often in very close proximity to the walls of vessels. In the pulp canal, most of the nerves remain associated with the vessels, although one or two fibres may leave the main bundle to continue on an independent course. Very infrequently single fibres approach the odontoblasts in the root region and occasionally small branches arise from these fibres, some of them passing between the odontoblasts towards the predentine.

The majority of the pulpal nerves pass uninterrupted, up the root canal towards the pulp chamber. Within the root canal the fibres occasionally divide, the branches continuing in the same direction as the parent fibre. Once the pulp chamber is reached – and this is especially evident in teeth with large pulp chambers such as molars – single fibres and small groups of fibres leave the main nerve trunks, spreading out towards the roof and walls of the pulp chamber (Fig 1C).

In incisor and canine pulp chambers the nerve fibres contained within the main nerve trunks hold to a fairly direct course towards the pulp cornu; those situated directly under the pulp cornu may pass without branching between the odontoblasts towards the dentine and appear to enter the dentinal tubules without changing direction. The very small conical areas of the pulp cornua seem to be the only situation on the crown where this happens to such a marked degree.

On approaching the 'cell-rich' zone adjacent to the 'cell-free' zone in the other regions of the pulp chamber, namely the walls and the roof of the pulp chamber between cusps, the majority of the nerves alter their course abruptly, often changing their direction several times. The angulation of the fibres in this situation seems to be random, the fibres turning off in all directions. In addition to changing their direction, many of the fibres divide, some quite frequently. This results in a complex interlacing 'basket-work' of fibres under the roof and walls of the pulp chamber, the plexus of Raschkow (Fig 1C). The fibres arising from the plexus of Raschkow cross the cell-free zone of Weil obliquely to reach the odontoblasts and then turn either abruptly between the odontoblasts towards the dentine or back towards the pulp.

From examination of the methylene blue and silver preparations, it is evident that the branching nerve fibres in the plexus of Raschkow have become reduced in diameter as a result of losing most of their myelin sheaths, although many of them still possess a Schwann cell covering. The variation of fibre sizes in the plexus of Raschkow ranges from 0·5μ to 2·0–3·0μ.

Most of the nerve fibres which pass between the odontoblasts change direction once more on reaching the predentine surface. Here there is a marked tendency for the fibres to divide into numerous branches. This plexiform arrangement

of nerves on the surface of the predentine is the marginal plexus referred to by Bradlaw (1936, 1939). Most of the marginal plexus is formed by naked axons which have a diameter of approximately 0·1μ–0·5μ. In the silver preparations these fibres have the distinctive morphology of small terminal nerve fibres. Some of the branches from the marginal plexus follow the odontoblasts into the dentinal tubules in the predentine; others become embedded in the substances of the predentine. Branches from these latter fibres may enter a dentinal tubule from the predentine and, changing direction, pass either towards the calcified dentine or back towards the pulp. Occasionally, among the fibres of the marginal plexus or those embedded in the predentine, a nerve fibre of larger dimensions with attendant Schwann cells may be found. These larger fibres nearly always loop back towards the pulp, although small branches may arise from them to enter the tubules (Fig 1 D, E).

In the dentinal tubules in calcified dentine of many specimens, small beaded fibres were found lying close to the process of the odontoblast, between it and the wall of the tubule. These fibres have a diameter of 0·2μ and less and the beads on them vary in size from 0·4μ–0·8μ. All these fibres are smoothly impregnated with silver and many can be followed in continuity with fibres of the marginal plexus. These fibres possess all the distinctive morphological characteristics of small terminal nerve fibres.

The validity of assuming that these silver impregnated beaded fibres are nerve fibres from a purely histological viewpoint has been fully dealt with in an earlier publication (Fearnhead 1957).

Although the intratubular nerve fibres often appear to be very closely applied to the surfaces of the odontoblast process, no synaptic or special form of connexion with the odontoblast process could be demonstrated. In fact, in sections where some shrinkage had occurred, nerve and odontoblast had become separated without apparent damage to the cell interfaces. This suggests that although there is an intimate contact between axon and odontoblast, there is no fixed organized connexion between them. It also refutes the idea that the intratubular nerve fibres penetrate the cell wall of the odontoblast to end intracellularly as suggested by Robertson (1891), Bernick (1948).

The intratubular fibrils that could be traced in continuity with nerves in the predentine or pulp were counted. There are many more nerves entering the dentinal tubules in the crown than in the region of the cervix. In the root, intratubular nerve fibrils were only occasionally seen. In all the fully formed teeth studied the general pattern of distribution was the same, although individual regional counts varied from tooth to tooth (Fearnhead 1957).

Although 312 teeth of various ages were studied this was not considered to be a large enough group from which quantitative conclusions could be drawn about differences in the peripheral density of the innervation between deciduous and permanent teeth. The number of nerves in the pulp is known to differ from tooth to tooth (Graf & Bjorlin 1951) and it is also quite possible that an increase in the density of the innervation of teeth may be related to age, disease, physical trauma or chemical treatment.

Although the junction between the enamel and dentine is especially sensitive, nerve fibres have been demonstrated within dentinal tubules for only a short part of their length. The question whether the peripheral portion of the dentine is innervated must, therefore, be regarded as still unsettled. Fernández-Morán (1952) and others have shown that submicroscopic nerve fibrils exist in the central nervous system and De Robertis & Sotelo (1952) have shown that the pseudopodal processes of neurites grown in tissue culture may possess submicroscopic extensions of their cytoplasm. It is quite possible, therefore, that terminal nerve fibrils too small to be resolved by optical microscopy may extend as far as the enamel-dentine or cementum-dentine junction as continuations of the intratubular fibres described in this work. It was hoped that silver deposited on the surfaces of such fibrils might bring them within the range of the optical microscope since silver deposited on nerve fibres during physical development may result in an increase in their diameter. In many of the silver preparations some of the dentinal tubules contained extremely thin fibrils very near the dentine-enamel junction (Fig 1F). These fibrils could not be identified as nerves with the light microscope, but it is possible that the greater resolving power of the electron microscope may help to elucidate their true character, when a reliable method for the fixation of dentine for electron microscopy becomes available.

Stewart (1927) cut the inferior dental nerve on one side of the jaw in cats in order to test the identity of the fibres demonstrated by the method used by Mummery (1916, 1924). Because unilateral resection of the nerve supply did not remove the fibres stained by Mummery's technique, he was able to show conclusively that the fibres described by Mummery were not nerve fibres. This type of experiment has

its greatest value when the fibres under consideration are not nerve fibres since, as they are not removed by the experimental procedure, they can be positively identified in both control and experimental sections. The reverse, that is a negative result, has not the same value, however, for although structures showing in the control sections may not be present in the section after the experiment, it is not always possible to say with certainty that they were present in the material on the experimental side before the experiment began. This has a special importance in the present case, since all the observations made on the innervation of dentine in this study point to the fact that the degree of innervation varies widely from tooth to tooth, even in different regions in the same tooth. It was, therefore, important to choose an experimental animal most likely to possess an innervation similar to that of man. Teeth from most of the common laboratory animals were examined histologically but monkeys were found to possess an innervation most closely comparable with that of man. All the features of innervation of the teeth of monkeys closely paralleled that of human teeth including the presence of intratubular dentinal nerve fibres (Fig 2A).

The right inferior dental nerve of a green monkey (*Cercopithecus sabæus*) was cut in its bony canal and a short length removed without damaging the accompanying inferior dental artery. The animal was sacrificed one month later, by which time it was hoped that complete degeneration of the resected nerves would have occurred. This, in fact, was the case, only a few isolated nerve fibres remaining in the pulps of the teeth on the operated side (Fig 2B, C). The plexus of Raschkow had disappeared and nowhere could beaded terminal nerve fibres be found in the position of the marginal plexus, in the predentine or in the tubules, whereas in the control material intratubular nerve fibres could be demonstrated. The fibres which remained after resection were of small diameter, were confined to the middle zone of the pulp tissue and were closely applied to the vessels; it was assumed that these were of autonomic origin which had escaped resection. It was considered, therefore, that the experimental section of the sensory nerve supply proved the validity of the histological criteria adopted for the identification of nerve fibre terminations in this study.

One of the most striking impressions gained from an examination of the human specimens obtained from patients in the older age group is the remarkable persistence of the nerve fibres of quite normal morphology which were frequently found enclosed in newly forming irregular secondary dentine. It is impossible to say how long these nerves, or those that often become embedded in predentine, survive in this situation.

Mohiuddin (1950) studied the degenerative changes in the nerves of deciduous teeth, which were about to be shed. He was able to demonstrate degenerative changes in the pulps of teeth in the process of being shed and suggested that these changes were confined to axons 1μ or more in diameter. Smaller fibres, according to this worker, apparently disappeared without any characteristic changes demonstrable with the silver method he used. He concluded that the onset of degeneration precedes root resorption and that this degeneration was confined to axons in the pulp and did not spread centrally to involve the axons in the main dental nerve trunks.

In the present study, some deciduous teeth were selected which, on the appearance of hæmatoxylin and eosin stained sections, were judged to have been well fixed. The roots of these teeth were fully formed and in some resorption had not begun; in others resorption had just commenced. Silver preparations of these teeth were examined to see whether there was any evidence that might support the hypothesis that 'spontaneous' degeneration occurs in human deciduous teeth just prior to resorption. Some nerve fibres were found in the resorbing teeth and the morphology of these fibres was similar to the morphological appearance described as a degenerative change by Mohiuddin, although many were apparently normal. However, some fibres possessing a similar morphology were also found in the teeth of the permanent dentition in which there was no evidence of resorption. It is considered that no special significance can be ascribed to these observations even if it could be proved that the changes were truly degenerative and not a result of fixation, since Weddell (1942) has shown that degenerating nerve fibres can nearly always be found in any group of otherwise normal preterminal nerves.

It seems, therefore, that there is little evidence to support Mohiuddin's claim that resorption is under nervous control, at any rate, in human teeth.

I wish in conclusion to make quite clear that this work only attempts to establish the presence of nerves in some of the tubules of calcified human dentine. It does not pretend to explain the mechanism involved in the transduction of a stimulus applied to the dentine, into an impulse carried by the nerve. Whether this occurs in the tubule or at the surface of the pulp or in both

places cannot be solved by a morphological study. One is, however, tempted to speculate a little and this I will do along a different line of thought.

It is impossible to examine the quite large amount of material studied in this work without gaining an impression of vital processes at work. Recently Hattyasy (1961) has come to the same view. Smoothness, beading, vesiculation, and growth cones have been observed in the tails of amphibian larvæ, by Speidel (1942), in different parts of the same nerve. It seems very likely, therefore, that these morphological changes in the axons are reversible ones which may be taking place all the time in all nerves, even in adults, and may represent axonal changes perhaps associated with changes in local environmental conditions.

Nerves that have entered the dental pulp have little chance of finding their way out again. The dental pulp, therefore, provides a very suitable region for the histological study of factors which might influence the peripheral density of nerve terminations. The nerve fibres, having once innervated the pulp, appear to continue their growth long after the tooth reaches its final form and to continue to grow after reaching what one would assume to be an adequate saturation of the tissue by sensory nerves. The view expressed by Weiss (1934, 1955) that the peripheral saturation of a tissue by terminal nerve fibres is under the control of some 'ordering factor' does not therefore seem to apply to tooth pulps, at least in man and many other mammals. The apparent 'overgrowth' of nerves in tooth pulps, giving rise to the plexus of Raschkow, might result from either the expression of an excessive growth potential, the absence of an inhibitory mechanism. Alternatively it may be that these nerves have the same growth span as other nerves, but since they are contained within a bony case they are not subjected to the same wear and tear processes which otherwise might normally cause a balance to struck between tissue loss and replacement.

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Section of Psychiatry

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Paper

Emotional Adjustment and Educational Achievement—the Preliminary Results of a Longitudinal Study of a National Sample of Children[1]

by J W B Douglas BM (*London*) and
D G Mulligan MA (*Edinburgh*)

This description of a longitudinal study of maladjustment in children is in two parts. One of us (J W B Douglas) gives the history of the study and discusses the educational progress of the children in relation to the number of symptoms of disturbed behaviour reported by the mothers. The other (D G Mulligan) describes some techniques developed during the last three years to measure maladjustment in these children and how he intends to validate them.

PART I

Dr J W B Douglas

Description of the Survey

This study of a sample of children born in the first week of March 1946 (*see* Douglas & Blomfield 1958) has a number of characteristics which make it suitable for the investigation of maladjustment. First, the 5,386 children enrolled in it still give an undistorted picture of all those of their age in Great Britain; there have been small losses which now, after fifteen years, amount to 10% of the children still living in this country, but they have not resulted in any serious distortion of the sample. Whenever the survey results have been compared with national figures – as for example, the allocation of grammar school places – they have shown the closest agreement. The fact that the sample may be taken as representative of the whole age group of children allows us to compare the behaviour of chosen groups – for instance, those attending child guidance clinics or those with educational difficulties – with national norms.

The second advantage of this study is that it is a longitudinal one started at birth. When we describe the early development of these children, the care they were given, the attitude of their mothers to early training, the bad habits, nightmares or other difficulties they may have had, we are using information that was collected contemporaneously and is not subject to the distortions and reinterpretations that bedevil retrospective surveys – and the same is true of our information on early separation of children from their parents, maternal employment and many other events that are commonly thought to be associated with disturbed behaviour in later life. Because the children are being kept under continuing observation we can see the permanency or impermanency of symptoms and we can test the value of different methods of predicting which children are likely to become maladjusted.

The information about these children comes from many sources; the mothers, teachers, school doctors, school nurses, and the children themselves have all contributed information to the survey and we see the same child through many eyes. This is perhaps best shown in the educational part of the survey where the opinions of mothers and teachers can be compared with the results of scholastic tests completed by the children and of the 11+ selective examinations which they sat.

The children in this survey are a sample of those born in Great Britain in the first week of March 1946 and were selected by taking all children from the middle class and the agricultural workers' families, but only 1 in 4 of the children from the manual working class families or the self-employed. In this way the number of children to be followed up was reduced to manageable proportions; at the same time the sample was enriched with middle class and agricultural workers' children who, from many points of view, are of

[1]This study is sponsored by a Joint Committee of the Population Investigation Committee, the Society of Medical Officers of Health and the Institute of Child Health (University of London). Funds have been provided at various times by the Nuffield Foundation, the Medical Research Council, the Population Council of America, the Ford Foundation and other bodies.

Table 1

Number of symptoms reported by mothers at 11 years – related to persistent earlier behaviour troubles (excluding bad habits, bedwetting, &c.)

	Boys				*Girls*			
Number of symptoms reported at 11 years	*Total numbers in sample*	*Numbers with a history of behaviour trouble* *Observed*	*Expected*	*Observed as % of expected*	*Total numbers in sample*	*Numbers with a history of behaviour trouble* *Observed*	*Expected*	*Observed as % of expected*
None	688	5	25·61	19·5	656	9	20·33	44·3
One	594	22	22·11	99·5	598	19	18·54	102·5
Two	255	25	9·49	263·4	206	13	6·39	203·4
Three or more	75	8	2·79	286·7	56	6	1·74	344·8
Totals	1,612	60 (3·722%)	60	100·0	1,516	47 (3·100%)	47	100·0

great interest (*see* Green 1954 for an analysis of the middle class male child and neurosis). When required we can regain the social structure of the original population of children by inflating the number of manual workers' and self-employed workers' children four times and when this is done we arrive at population estimates of mortality, fertility, etc., which check closely with those from national sources.

During the fifteen years of this study the homes were visited by school nurses or health visitors on ten occasions and the mothers were asked among other matters, about early milestones, breast-feeding, bladder and bowel training methods, and symptoms such as nail-biting, thumb-sucking, feeding difficulties, nightmares and bedwetting which may indicate difficulties of adjustment. The teachers have reported on the children four times. On the first occasion, when the children were aged 6, the information the teachers gave was entirely concerned with progress at school but on the second occasion, at 10, they answered questions on their attitude to work, reaction to discipline, and relation with their school mates. On two occasions since then, we have asked them to report in considerable detail on the children's behaviour in school. The doctors have given these children four special medical examinations, during the course of which they reported on bitten nails and attendances at child guidance clinics, and gave them a thorough clinical examination lasting, on the average, more than half an hour. The children themselves have taken three batteries of mental ability and school achievement tests specially designed for this study by the National Foundation for Educational Research in England and Wales and they have also completed two short questionnaires and a psychological inventory.

All this amounts to a considerable mass of data which are stored on Hollerith cards from which we can rapidly build up special cards to give a complete account of any special aspect which we wish to study. There are approximately half a million cards from which we can draw and without these mechanical aids this study would not have been feasible.

We have studied the number of symptoms of disturbed behaviour reported by the mothers when these children were 11 and their educational progress as shown by their teachers' reports, their performance in our own tests at 8 and 11 and the results of the 11+ examination[1]. This information is based on 3,128 children attending Local Education Authority schools in England and Wales who took their 11+ examinations in 1957. Scottish children are excluded because they are selected for secondary schools at a different age and in a different manner. Private school children and those who are educationally subnormal are also excluded because they are not subject to the normal selection procedure.

Symptoms Reported by the Mothers

For this preliminary study I selected four groups of symptoms reported by the mothers to the school nurses who visited them just before their children reached their eleventh birthday. These symptoms were (*a*) habits such as nail-biting, nose-picking or thumb-sucking, (*b*) bedwetting, (*c*) nightmares, and (*d*) recurrent unexplained abdominal pain or vomiting. They were selected because they appear to be related to disturbed behaviour at school and at home. For example 0·1% of children with none of these four groups of symptoms have attended child guidance clinics, as compared with 5·4% of those with three or more symptoms. Similarly, relatively few of the mothers whose children are symptom free at 11 have at any previous time been worried about their behaviour[2]; but as the number of the reported

[1] A more detailed study of behaviour and school achievement will be found in a forthcoming publication on secondary selection.

[2] The mothers were specifically asked at each home visit whether they were worried about their children's behaviour and if so for what reasons.

symptoms increases so does the proportion of children with earlier behaviour troubles as is shown in Table 1.

Early behaviour troubles increase steadily as the number of symptoms reported at 11 years increases. Children who are symptom free at 11 are less than half as likely to have a history of behaviour troubles as the average child, while those with three or more symptoms are more than three times as likely to have such a history.

A similar number of symptoms were reported by middle-class and manual working-class parents and there is no reason in the following tables to take account of the social class of the children. Rather fewer symptoms were reported for the girls than the boys, only 15% of the middle class girls and 19% of the manual working class girls have more than two, as compared with 20% each of the middle class and the manual working-class boys. The favourable position of the middle-class girls is entirely explained by the low incidence of bedwetting among them. This was noted at earlier ages (Douglas & Blomfield 1958) and persists at 11. For this reason, and also to show the internal consistency of the results, I have shown boys and girls separately in the following tables[1].

Evidence from two independent sources at first sight suggests that the children with several reported symptoms tend to be emotionally disturbed. The first comes from comments volunteered by their teachers when they were 10 years old. In an open question at the end of a school progress questionnaire asking for further comment from the teachers 131 children were said to be sensitive or highly strung. These are the children who tend, one year later, to be reported by their mothers as having several symptoms of disturbed behaviour.

Table 2

Children with few and with many reported symptoms – related to scarring and disfigurement

Number of reported symptoms	*Number scarred or disfigured as % of number expected (numbers expected in brackets)*		
	Boys	*Girls*	*Both sexes*
None or one	91·4 (27·3)	75·0 (20·0)	84·4
Two or more	134·9 (6·67)	226·7 (3·97)	169·2

The second piece of evidence comes from children who are severely scarred or disfigured from, for example, birth marks, accidents or in one instance a dog bite. It is to be expected that disturbances of behaviour would be more common among these children, particularly if they are girls, and this might be shown by the number of symptoms reported by their mothers at 11 years. This expectation, as Table 2 shows, is fulfilled.

Scarring or disfigurement is more commonly observed among those with several symptoms than among those with few. This observation would, of course, be explained if the mothers of these children were worried about their emotional adjustment and so noticed symptoms which they would not otherwise have reported (we have previously described an instance of such selective reporting: Douglas & Blomfield 1958, p.131), but if so the additional symptoms noticed would be the vaguer ones such as nightmares, bad habits or abdominal pain, rather than bedwetting which could hardly be overlooked. The fact that bedwetting is no more common among the scarred or disfigured children than among the rest suggests that this explanation is indeed correct.

Table 3

Children with few or with many reported symptoms – related to their achievement at primary school

	Number of reported symptoms	*Number observed in category as % of number expected (numbers expected in brackets)*		
		Boys	*Girls*	*Both sexes*
Hard workers●	None or one	110·9 (129·9)	106·6 (219·6)	108·2
	Two or more	58·7 (34·1)	69·1 (46·3)	64·7
Expected to get grammar school places●	None or one	105·9 (354·0)	103·9 (423·3)	104·9
	Two or more	77·6 (94·4)	80·2 (84·8)	78·8
Awarded grammar school places	None or one	104·8 (339·6)	106·2 (361·5)	105·5
	Two or more	81·2 (87·4)	70·2 (75·5)	76·1

● Teachers' assessments before child sat 11+ examination.

Educational Progress of these Children

The children with several symptoms are more often absent from school than those with few and their mothers tend to be worried because they often are making slow progress with their work. Their teachers see them as frequently lazy, unable to concentrate and undisciplined.

According to their teachers the children with few symptoms are harder workers and more

[1]For simplicity I have compared children who have one or no symptoms with those who have 2 or more and for the same reason have shown only the percentage ratio of observed to expected numbers and, in brackets, the numbers expected. From these and the marginal totals of Table 1 the basic figures of each subsequent table can be reconstructed.

likely to get into grammar schools than those with many symptoms, and the results of the 11+ examinations confirm this view. Grammar school places are given to 5% more of those with few symptoms than we should expect and to 14% fewer of those with many symptoms. The teachers' estimates of ability are in close agreement with this, taking into account that they tend to overestimate their pupils' chances. The 11+ examinations show the girls with several symptoms as being at a greater disadvantage academically than the boys with several symptoms (*see* Table 3) but this is not the view of the teachers.

The poor showing in the secondary selective examinations of the children with several symptoms is partly explained by their performance in our tests of mental ability and school achievement. It will be seen in Table 4 that there is a progressive decline in measured ability as the number of reported symptoms increases and that the girls are more affected than the boys. Moreover, the test performance of the children with few symptoms improves as they get older (between 8 and 11 years) but the performance of the children with many symptoms deteriorates.

Table 4

Number of symptoms reported by mothers at 11 years – by average score in school achievement tests and change in score between 8 and 11 years

Number of symptoms reported at age 11	*Average T scores at 11 years*●			*T scores at 8 years*	*Improvement (+) or deterioration (–) between 8 and 11*
	Boys	*Girls*	*Both sexes*	*Both sexes*	
None	51·97	52·54	52·25	51·82	+0·43
One	51·45	52·17	51·82	51·53	+0·29
Two	51·10	50·35	50·77	50·91	−0·14
Three or more	49·14	46·94	48·21	49·41	−1·20

●The T scores have an average of 50 for the whole survey population (adjusted for sampling) and a standard deviation of 10. The figures in this table are the mean of four tests – of mental ability, reading, vocabulary and arithmetic at 11 years and of mental ability, reading, vocabulary and sentence completion at 8 years. The same reading and vocabulary tests were used at 8 and 11

The poor test performance of the children with several symptoms is insufficient to explain their disadvantage in the 11+ examination. At each level of measured ability they are less likely to get a grammar school place than are those with few symptoms, and the extent of their disadvantage may be summarized by saying that they get 10% fewer places than expected after taking their measured ability into account, whereas the children with few reported symptoms get 2% more places.

Conclusions

When children are grouped, on the basis of their mothers' reports, into those with few symptoms of disturbed behaviour and those with several symptoms, those with few symptoms do better in tests of school achievement and gain more grammar school places in the secondary selective examinations. They are also more favourably assessed by their teachers, who say they work harder and are academically more able than the children with several reported symptoms, and their mothers are seldom worried about their progress at school. Whereas the test performance of the children with few symptoms improves somewhat as they grow older, that of the children with several symptoms deteriorates. The latter gain fewer grammar school places than their performance in the tests would lead us to expect and it seems that the tests measure only a part of their academic handicap – perhaps the more searching procedure of secondary selection shows up deficiencies in habits of work and concentration that the shorter tests fail to show.

PART II

Mr D G Mulligan

The aim of this part of the enquiry is to place each survey child in one of a number of empirically derived groups, dependent on his level of 'emotional and social adjustment', and to relate these groups to such factors as educational record, sex, social class and circumstances of upbringing. Unfortunately, diagnostic criteria of maladjustment are uncertain, and no methods of proven worth have been devised for its measurement.

It would not have been wise to use attendance at a child guidance clinic as the sole means of defining maladjustment. Only a very small proportion of the survey children – 9 in every 1,000 – have at any time been either enrolled in clinics or placed under psychiatric care. The average of the estimates of *prevalence* of maladjustment from the three pilot surveys associated with the Underwood Committee enquiry (1955) is that about 80 in every 1,000 school children need treatment at any given time. It may be objected that the Underwood Committee estimate is exaggerated, but American studies of the prevalence of maladjustment amongst school children have given similar results (Wickman 1928, Rogers 1942, Ullman 1952, Glidewell *et al.* 1960). It seems that there are many emotionally disturbed children whose problems go unnoticed.

Although, as we have already mentioned, diagnostic criteria of maladjustment are uncertain, it was decided to examine the survey sample for those characteristics maladjusted children are commonly said to show and to define maladjustment in terms of symptoms, the two following

assumptions being made: (*a*) Children who present many symptoms are more maladjusted than those who present only a few, (*b*) children who present particular symptoms to a marked or excessive degree are more maladjusted than are those who show the same traits to a lesser degree.

The symptom-list given in the Underwood Committee Report was used in constructing a questionnaire for the teachers of the survey children. Some symptoms in the list were excluded because teachers judged they would have little or no opportunity of observing them; others because it was felt that, if included, they might provoke irritation.

The questionnaire was sent to the schools during May 1959; it contained 29 items, 22 of which were in the form of rating scales. The survey children were then 13 years and 2 months old.

To supplement the information from the teachers we decided to get the children to fill in a self-reporting inventory. As Eysenck's analysis of neuroticism amongst adults suggests the importance of the relationship between the orthogonal factors of 'emotionability' and 'extraversion–introversion' on the one hand and both specific symptoms and groups of symptoms on the other (Eysenck 1952), it was proposed that scores on 'emotionability' and 'extraversion' should be obtained for each child to see how the symptoms reported by teachers clustered around these two axes. These scores would also serve the further purpose of providing some check on the validity of the teachers' assessments.

The Pintner questionnaire (1938), which purports to measure three independent traits – 'ascendance-submission', 'extraversion-introversion' and 'neuroticism' (or 'emotionability') – was subjected to two short analyses. Originally containing 105 items it was reduced to the 15 best discriminators in each section. The ascendance-submission scale having an r of 0·49 with extraversion was replaced by a scale purporting to measure 'aggressiveness'. The inter-correlations between the three scales in their final form calculated from the scores of 120 13-year-old children were:

Aggressiveness–extraversion	$r-0{\cdot}08$
Aggressiveness–neuroticism	$r+0{\cdot}69$
Extraversion–neuroticism	$r-0{\cdot}14$

The extraversion scale would appear to be independent of the other two scales – which is in line with the findings of Eysenck. It will be interesting to see whether those children whose teachers' reports suggest that they are suffering from nervous disorders are, when measured by the Pintner scales, both neurotic and introverted; and whether those children whose teachers' reports suggest they show some form of behaviour disorder are both neurotic and extraverted.

The Pintner questionnaire was also filled in by the survey children during May 1959.

The results of the 1959 questionnaires have been punched on Hollerith cards and frequency counts of specific symptoms have been made.

According to teachers' reports, sex differences in individual symptoms were not striking, though the general trend, as has been found in most Wickman-type studies, was for the boys to receive less favourable ratings than the girls. More boys than girls were said to show nervous habits; they lied, cribbed and played truant more often and their attitudes to school work were rated less favourably by their teachers.

The number of unfavourable ratings made by the teachers were totalled, giving a rough maladjustment score for each child: 1,232 (30%) of the 4,109 children received no unfavourable ratings from their teachers; 442 (8%) received 7 or more unfavourable ratings; and 184 (4·5%) received 10 or more unfavourable ratings.

The children were allocated to their respective social classes – the classification used being based on the occupation and education of each survey child's father and grandparents, giving four social classes in all. For most items in the questionnaire there was a slight tendency for children in the two lower social groups to receive less favourable ratings than those in the two upper social groups and, as one would expect, it was on those items conerning the child's attitude to schoolwork that the largest differences were found.

The social class differences become more definite when the symptoms reported by the teachers are totalled for each child. Of the upper middle-class boys 7% are reported by their teachers to show 7 or more symptoms compared with 15% of the lower working-class boys. The same holds true for the girls: 4·5% of the upper middle-class girls compared with 12% of the lower working-class girls are reported by their teachers to show 7 or more symptoms.

What is essentially found in these ratings is a measure of the reputation of the child in the eyes of his teacher; a measure which may, of course, bear no relation at all to the mental health of the child. Thorpe (1959), for instance, has reported that teachers' *global* assessments of maladjustment among school children are not related to scores on objective tests previously shown to distinguish neurotic from normal children. However, Glidewell *et al.* (1960) found good agreement between teachers' ratings of maladjustment amongst school children and assessments made by trained mental health workers. Findings on this point are conflicting.

There is a further problem. Maladjusted children presumably differ both in kind and

degree. A score based simply on the number of maladjustment signs reported by teachers does not take into account the relative diagnostic significance of individual symptoms, nor does it allow the principal types of maladjustment to be distinguished from one another. So, to test the validity of the children's questionnaire and to learn the most efficient means of scoring the teachers' questionnaire, a special study was carried out.

186 children, receiving treatment at child guidance clinics, were selected from four areas[1]. None of these children had been enrolled in the national survey sample but all were attending ordinary schools – that is, they were not at approved schools or special schools for maladjusted children.

Clinical psychologists, familiar with the problems of these children, were asked to group them according to the symptoms they exhibited; nervous and withdrawn children and aggressive and troublesome children were listed separately from each other and the rest.

The two questionnaires were sent to the various schools where they were completed by the child guidance children and their teachers; the average age of the child guidance sample at the time of testing was 13 years 1 month, and the age range fell between 12 years 2 months and 14 years 2 months.

Completed and usable sets of questionnaires were returned for 161 children – 105 boys and 56 girls. Of the boys, 46 had been classified by clinicians as aggressive and troublesome, 50 as nervous and withdrawn and 9 had been left unclassified. Of the girls, 25 had been classified as aggressive and troublesome, 25 as nervous and withdrawn and 6 had been left unclassified.

The child guidance children were then matched on four variables – sex, father's occupation, Local Authority area, and intelligence – with an equal number of children in the national survey sample and comparisons between the two groups on both the teachers' and children's questionnaires were made.

The child guidance sample had a mean score of 12·92 when the 'aggressive' and 'neuroticism' scales in the children's questionnaire were combined, compared with a mean score of 10·22 for the matched controls – a difference of 2·70, which is highly significant.

The mean number of unfavourable teachers' ratings was calculated for the various groups of maladjusted children and their controls. The 161 child guidance children received on the average 7·57 unfavourable ratings, whereas the comparable figures for the control group and the national survey sample were 2·57 and 2·43 respectively. Child guidance children, classified by clinicians as aggressive and troublesome, were more severely rated by their teachers than those classified as nervous and withdrawn (a mean of 8·54 compared with 6·63 unfavourable ratings); and it would seem that, amongst maladjusted children, aggressive girls are the most conspicuous in the classroom – they received on the average over 9 unfavourable ratings from their teachers.

When the 29 items in the teachers' questionnaire were looked at singly, differences were found between the child guidance children and their controls on all items apart from one. A question on daydreaming failed to differentiate maladjusted from normal girls, though a significantly higher percentage of child guidance boys than their controls were rated 'frequent daydreamers' by their teachers.

These comparisons between the maladjusted and control children on the teachers' questionnaire do not provide definite evidence that school teachers are perceptive about the emotional and social problems of their pupils. The child guidance sample was a selected group, marked off from other children if for no other reason than simply by the fact that they were receiving treatment at child guidance clinics. We do not know what proportion of the teachers, who provided ratings for the maladjusted children, actually knew that their pupils were enrolled at child guidance centres, but those who were aware of that fact may have been either (*a*) less cautious in making unfavourable ratings than teachers whose children were not child guidance attenders, or (*b*) more vigilant, more on the look out for signs of emotional stress in their pupils. In other words, the data may be contaminated.

Within the child guidance sample itself, however, more valid comparisons can be made. Clinicians who classified the maladjusted children into two principal groups – namely, the aggressive and troublesome and the nervous and withdrawn– were asked to do so on the basis of their personal experience with each child and not simply in terms of the reasons for which the child had been originally referred. It was hoped that, in this manner, the assessments of a child made by both clinicians and teacher would be independent of one another even if the teacher had been instrumental in sending the child to the clinic in the first place.

When comparisons were made within the child guidance sample it was found that maladjusted children, both boys and girls, classified by their clinicians as aggressive and troublesome, re-

[1]We wish to thank the Directors of Education and the Senior Educational Psychologists in Dundee, Glasgow, Leicester and Middlesex for their help in acquiring this sample.

ceived less favourable reports from their teachers than nervous and withdrawn children on 11 items; they were rated as poorer workers, having less power of concentration, more untidy in class work, more often disobedient, presenting greater disciplinary problems to their teachers, more restless in class, more rough during playtime, more likely to 'show off' and seek attention, more likely to become unduly resentful when criticized or punished, more likely to crib and more likely to become aggressive and quarrelsome than the nervous and withdrawn children.

On the other hand, nervous children were reported by their teachers to be less popular, more frightened by rough games, more likely to avoid attention – hating being in the limelight, more often friendless and more likely to become unduly miserable and worried when criticized or punished than the aggressive and troublesome children.

It seems that there is some measure of agreement between the teachers and the clinicians in their descriptions of maladjusted children.

As we have already mentioned, one of the purposes of this special study was to learn the most efficient means of scoring both the children's and teachers' questionnaires. What we need to know is how to weight the items in both questionnaires according to their power in discriminating maladjusted from mentally healthy children, and how to weight the items according to their power in distinguishing, amongst a maladjusted group, those children who are nervous and withdrawn from those who are aggressive and troublesome. A form of discriminant function analysis, applied to the child guidance sample and their controls and done separately for boys and girls, has been selected for this purpose. It is hoped that by this means two scores will be derived for each questionnaire – one score distinguishing the aggressive children from both the nervous and normal groups, the other separating the nervous children from both the normal and aggressive groups. The questionnaires for the national survey children would then be scored according to the sets of discriminant weights, and an estimate of the validity of the teachers' scores could be made by correlating them with those obtained from the children's questionnaire.

During February 1961 the teachers' questionnaire was again sent to the schools of the survey children – twenty-two months after its first administration. It is unlikely that many of the teachers who filled in the questionnaire on the first occasion have been called upon to do so again, but we will be able to check this.

A new sample of child guidance attenders – this time 15 years of age – will be used, together with matched controls, to cross-validate the scoring system derived from the discriminant function analysis based on the earlier sample. If the system of weighting items in the teachers' questionnaire stands up to cross-validation the 1961 teachers' reports will be scored in the same way as the 1959 material. This will leave us with scores distinguishing, according to the teachers' ratings, the maladjusted from the adjusted children at two different periods during adolescence; and we shall be able to pick out from the survey sample those children who have received unfavourable reports from different teachers on separate occasions.

As it is unlikely that all emotionally disturbed children manifest their problems in the classroom or that all teachers are equally able to recognize signs of maladjustment in their pupils, we have supplemented the information from the 1961 teachers' questionnaire by asking the mothers of the survey children to report on the behaviour of their children at home. By correlating these judgments of the mothers with the teachers' ratings we shall have a further opportunity to assess the perceptiveness of school-teachers in picking out maladjusted children.

Finally, we shall be in a position to select from all the material available on the survey sample those unfortunate children whose problems appear to be perennial: those who were reported by their mothers to have symptoms at ages 6, 9 and 11, who made high scores on the 'neuroticism' questionnaire, who were rated unfavourably by their teachers at 13 and by both their teachers and mothers at 15.

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Section of Obstetrics and Gynæcology

President W R Winterton FRCOG

Meeting April 28 1961

Chromosome Abnormalities and Nuclear Sexing

Professor T N A Jeffcoate (*Liverpool*)

A Clinician's Concept of Intersex

Knowledge of the factors which determine sex is increasing so rapidly that any over-all concept of intersex can be no more than tentative, and needs to be kept fluid. With these qualifications, this communication is concerned with aberrations in physical sex present at birth. Modifications of sex which may develop later in the adult as a result of feminizing and masculinizing tumours are excluded, as are psychological disturbances such as trans-sexuality, transvestism and homosexuality.

Three overriding principles govern the understanding and practical management of physical intersex: (1) Every individual is bisexual in varying degrees and only relatively gross departures from the normal can be classified as significant states of intersex. The dividing line is a matter of opinion; thus hypospadias in an otherwise normal male may or may not be accepted as feminization of the external genitalia. (2) There are no absolute criteria for diagnosing the sex of an individual, not even the nature of the gonad, the chromatin pattern in the nuclei, or the number and type of sex chromosomes. More important than these signs, both from the standpoint of the individual and of the community in which the individual lives, are the secondary sex characters such as the external genitalia, breasts, voice and facial hair. It follows that the terms hermaphroditism and pseudohermaphroditism, male or female, previously used for denoting types of intersex should be abandoned; they imply acceptance of the nature of the gonad as a criterion of sex. (3) Femininity is a state which approaches that of the neuter, and masculinity is the result of a positive influence superimposed on this state. If the gonads are destroyed at an early stage in fœtal life, then, no matter whether they be testes or ovaries, the genital ducts always develop in a female fashion. Removal of testes after birth also tends to make an individual feminine whereas removal of the ovaries has no effect on femininity.

Types of Intersex and their Mechanism

Many factors take a part in determining sex *in utero* but none is all-powerful and decisive. The action of each can be modified by that of others. This explains why intersex presents in many forms.

Chromosomal sex: Sex is primarily determined by the number and type of chromosomes contributed by the ovum and the spermatozoon at the time of fertilization. The nucleus of the normal mature ovum carries one X chromosome and this is joined by either one X or one Y chromosome contributed by a spermatozoon. The result is a zygote with either XX (female), or XY (male), chromosomes. As the fertilized ovum undergoes segmentation, the nucleus of each daughter cell should receive either XX chromosomes or XY chromosomes depending on the sex of the embryo. It therefore might be expected that every cell of all the tissues of the adult would show the same chromosomal arrangement; this may be true for the majority of cells in the normal male or female but there are exceptions and the extent and frequency of mosaicism remains to be decided.

There may, however, be an abnormal number of sex chromosomes and this occurs as a result of their faulty or unequal distribution during cell division either before or after fertilization. Thus, 'non-disjunction' of the two chromosomes during reduction division of either gamete can result in an individual whose make up is XO, XXY, XXX or YO. The last is only hypothetical or lethal but the others are found in gonadal dysgenesis (Turner's syndrome); primary micro-orchidism (Klinefelter's syndrome) and the so-called 'super female'. Inequality in the distribution of chromosomes during cell division also arises from phenomena such as translocation, duplication and deletion, and results in various patterns such as XXXX and XXXY. The sex chromatin is positive whenever there are two or more X chromosomes present in a nucleus, and this irrespective of its Y content. If only one X chromosome is present the test is negative. Thus the XX, XXX and XXY arrangements give a positive test, while XY and

XO result in a negative test. From the clinical standpoint, however, and in keeping with the principle first enunciated, it has to be recognized that Y is a positive masculinizing force so, whenever it is present, the individual presents physical features of masculinity. The XXY pattern therefore gives a positive chromatin test in an individual who nevertheless looks essentially male.

When chromosomes become unequally distributed during segmentation after fertilization, only part of the embryo may be affected. Certain tissues or cells in the adult then show a chromosome pattern different from that of others. This phenomenon of mosaicism may be present to some extent in all individuals without producing significant clinical effects. Sometimes, however, it is seen in gross forms.

Case 1 A girl, aged 16, complaining of primary amenorrhœa, had normal female genitalia, the development of which suggested that menstruation was imminent. The breasts were forming well. She had, nevertheless, long ape-like arms and legs covered with a thick growth of hair, features which had been present at birth, and throughout childhood. The hands and feet were also large and masculine if not anthropoid, and scalp hair was continued over the temples to the eyebrows. According to oral smears this individual is chromatin positive and a count based on cultures of leucocytes indicated a normal XX sex chromosome complement. But skin taken from the arms, trunk and legs showed chromatin-negative nuclei. Unfortunately, tissue cultures of these skins failed and their chromosomes make up is so far unknown. Nevertheless, on the evidence so far available this girl may be an example of gross mosaicism. Her parents are apparently normal and so is her sister, aged 20.

[Her first period began on 28.4.61, the day of the meeting, and the cycle has since been regular.]

Genetic sex: The chromosomal drive towards sex can be strong or weak, and presumably depends on genes distributed on the X and Y chromosomes. But, in addition, there are sex-influencing genes on the autosomes. These, which are mainly masculinizing, can modify the chromosomal urge towards sex differentiation. The effects of these autosomal genes depend partly on their inherent force and partly on the strength of the basic sex chromosomal urge. Thus a weak sex chromosomal influence is more easily modified.

Minor autosomal genetic masculinizing influences in an otherwise normal female probably account for 'constitutional' hirsutism. It is thus not surprising that this common syndrome shows a strong familial and inherited tendency.

A relatively powerful autosomal genetic influence, operating at an early stage in embryonic development, can interfere even with the differentiation of the gonad, and probably explains those cases in which an individual has ovo-testes, or a testis on one side and an ovary on the other. As might be expected, such a finding is generally, although not always, associated with a positive chromatin test, suggesting an XX chromosomal complement. The phenotype (general outward appearance) may be female or male.

Case 2 (reported by courtesy of Dr M M de la Harpe of South Africa). A man had apparently normal external genitalia except that only one testis was descended. Laparotomy revealed that, on the other side, he had an ovary and a unicornuate uterus with tube. The ovary contained a recent corpus luteum. His chromatin sex was positive.

Case 3 (Case of Dr F P Hudson and Miss Isabella Forshall). **P B**, aged 3 weeks and registered female, was found to have external genitalia which appeared male except for hypospadias. The internal genitalia were entirely female but section of one 'ovary' showed an ovo-testis. Oral smears: chromatin-positive nuclei.

Sometimes, and again presumably due to powerful autosomal genetic urges, the chromosomal drive towards gonad differentiation can be completely reversed.

Case 4 A girl aged 20, an international woman athlete, complained of deepening of the voice and primary amenorrhœa. She had a large hypospadiac phallus with a urogenital vagina behind. Above this, the müllerian ducts had not developed and the undescended gonads were testes. Yet examination of both oral smears and skin showed that she was unquestionably chromatin positive.

The Organizing Power of the Gonad

Irrespective of chromosomal and genetic drives, sex differentiation *in utero* is to some extent controlled by the organizing power of the gonad. Indeed the development of the gonad is itself dependent on the presence of primitive germ cells which determine whether the gonadal mesoderm shall differentiate into granulosa cells or testicular tubules. Without these germ cells, as in Turner's syndrome, the gonad remains asexual. The gonad in turn controls the persistence or degeneration of the müllerian and wolffian ducts but, in this respect, the testis is much more important than the ovary. It is the presence of a testis rather than the absence of an ovary which accounts for the male genital tract on the one side of Case 2. Moreover, it is the absence of the testis rather than the presence of the ovary on the other side which allowed the corresponding müllerian duct to persist and the wolffian duct to atrophy.

When aberrations in genital duct development do accompany unilateral cryptorchidism they usually occur only on the affected side. Rarely, however, both müllerian ducts persist even though only one testis is functionless.

Case 5 An apparently normal man, married with two children and proved to be fertile by semen analysis, had only one well-formed scrotal testis. On the other

side he developed an inguinal hernia and within the sac was found a complete uterus with two fallopian tubes and one rudimentary undescended testis.

Combined Gonadal and Genetic Causes of Intersex
In practice it is common to see individuals who have a male (XY) sex chromosome complement yet whose genitalia show varying degrees of femininity. In these it is usually impossible to say whether it is weak masculinizing genetic influences of the autosomes and the Y chromosomes or failure of the gonad-organizing capacity which is responsible. It is likely that both are concerned in many of these cases. Thus failure of a testis to descend and to function may well be genetically determined. An associated disturbance of the development of the genital ducts, the phallus and the urogenital sinus may then be either the result of the testicular failure or of adverse genes. The condition of hypospadias occurring in an otherwise normal male shows a strong familial and inherited tendency. Yet a similar abnormality is commonly associated with cryptorchidism.

Many clinical variants are possible and all tend to be familial. Despite well-developed and descended testes in a bifid scrotum, the phallus can be rudimentary as well as hypospadic. When hypospadias is associated with cryptorchidism, the müllerian ducts are usually atrophied but may persist to give rise to fallopian tubes, uterus and vagina. Even if these ducts do not develop, the urogenital part of the vagina can be present. Again, postpubertal sex differentiation in these XY individuals suffering from abnormal genetic and gonadal influences is variable. Some remain effeminate even to the extent of gynæcomastia; others develop a masculine voice with or without facial hirsuties.

Case 6 I A, aged 16, and brought up as a girl, complained of primary amenorrhœa. Her voice was beginning to 'break' and the breasts showed no signs of enlargement. The facial and bodily hair distribution, however, was normal. Behind a large hypospadic phallus was a well-developed vagina. Laparotomy revealed a normal though infantile uterus with two fallopian tubes. In the position of the ovaries were testes. At least, a testis with a histological appearance typical of cryptorchidism was found on one side, while sections of the other gonad showed connective tissue only. This particular patient, whose chromatin pattern was negative but whose chromosome count is unknown, may well represent a mixed syndrome. That her uterus was functional was easily demonstrated by the fact that, after gonadectomy, œstrogen withdrawal bleeding was induced quite regularly. Moreover, this treatment resulted in good breast development.

Cases 7 and 8 A W, aged 2½, and S W, aged 4½, were born of the same parents and registered as girls. In both cases the phallus was insignificant and the external genitalia looked female. There was, however, no sign of a vagina or of müllerian duct tissue, and the chromatin sex was negative. S W was operated on for bilateral hernia at the age of 2½ and the testes found in the sacs were returned to the abdomen. The younger child had rudimentary testes in the inguinal canals and these were removed.

Both children are being kept socially female, and it now remains to be seen whether the one with intra-abdominal testes develops more masculinity or more femininity than the one who is neuter. This observation will be of importance because it is often alleged that undescended testes in an apparent female should not be removed, at least not until after puberty, because they contribute to the development of female secondary sex characters.

Feminizing testes: In this syndrome an apparent female has well-developed breasts and a normal vulva. She is usually attractive in appearance and typically has a smooth and hairless skin. Even the axillæ and the pubes usually remain more or less hairless, this probably being an associated defect and not the result of a hormonic disorder. The vagina may or may not be present, and so may the uterus. The chromatin pattern is negative and chromosomal arrangement is usually XY. The syndrome shows a familial tendency, the taint being mostly transmitted maternally. It is presumed to be due to a sex-linked recessive gene or to a sex-limited dominant autosomal gene. The mechanism of feminization, however, is generally attributed to a weak androgenic function of the testes. Indeed, it is said that these organs produce considerable amounts of œstrogen and that this is borne out by the finding of large clusters of actively secreting Leydig cells. So it is reported that removal of the testes leads to loss of femininity, regression of the breasts and even hot flushes.

Case 9 A G, aged 16, also presented the typical clinical features of testicular feminization, was chromatin negative and had only the urogenital part of the vagina present. Vaginal smears showed a strong œstrogenic effect. One testis had been removed from a hernial sac at the age of 5 years. This patient's sex interest was toward boys and she admitted practising coitus regularly. She was an outstanding woman athlete covering 100 yards in 11 seconds. Removal of the testes in this case undoubtedly had some effect. Her time for the 100 yards changed to 12·8 seconds, she increased 7 lb in weight, and lost interest in her 'boy friend'. She thought that she might have experienced some hot flushes and sweats but the breasts remained well developed. The cause of these reactions is difficult to assess because, despite advice to the contrary, the parents informed the girl that testes had been removed. This inevitably resulted in considerable emotional upset which may in part explain some of the post-operative changes.

The urinary excretion levels found in hormone assays (Dr I F Sommerville) were as follows:

	Before operation (72-h specimen)	*5 months after operation (3 assays)*		
Œstradiol (μg/24 h)	1·2	1·6	2·1	1·6
Œstrone (μg/24 h)	4·1	2·1	1·7	1·8
Œstriol (μg/24 h)	14·0	3·0	5·2	1·5
17-ketosteroids (mg/24 h)	24·5	14·5	18·0	15·6
17-ketogenic hormones (mg/24 h)	18·5	11·0	14·7	18·8
Pregnanediol (mg/24 h)	0·3	1·4		0·4
Pregnanetriol (mg/24 h)	0·95	1·7		1·7

Case 10 S C, aged 18, and chromatin negative, complained of primary amenorrhœa. She presented the typical features of the syndrome. The external genitalia were female but hairless and a vagina measuring 4 in. was present. Vaginal smears showed a strong œstrogenic effect. Laparotomy, however, revealed no sign of müllerian ducts other than a transverse fold in the pelvis. Testes with associated epididymides were removed from the side walls of the pelvis. Sections of the gonads showed the typical appearance of hypoplastic tubules with well-formed islets of active interstitial cells. The operation was performed eighteen months ago and, since then, the girl has not had hot flushes or any untoward symptoms; nor have the breasts atrophied. Indeed, she is now engaged to marry. Results of hormone assays (Dr I F Sommerville) were as follows:

	Before operation		*After operation*						
	(2 assays)		*2 months (3 assays)*			*6 months (3 assays)*			*One year (72-h specimen)*
Œstradiol (μg/24 h)	2·3	2·0	1·6	1·2	>1·0	3·4	1·9	>1·0	2·1
Œstrone (μg/24 h)	3·0	5·9	1·0	1·5	2·5	1·8	3·9	1·8	3·5
Œstriol (μg/24 h)	10·9	2·1	10·1	3·3	4·0	2·3	1·9	>1·0	7·8
17-ketosteroids (mg/24 h)	25·4	21·1	12·4	18·9	13·4	7·0	20·3	9·0	9·7
17-ketogenic hormones (mg/24 h)	11·9	12·4	8·6	3·7	11·2	15·4	13·9	5·7	15·2

The hormone assays in Cases 9 and 10 are remarkable in that they show pre-operative excretion levels of both œstrogens and 17-ketosteroids which are within the normal range for the male. Moreover, in both cases the 17-ketosteroid excretion fell after orchidectomy to within the female range. This suggests that the androgenic function of the testes was not below normal. In Case 10, the excretion levels of all the œstrogens, although showing wide daily variations, do not appear to have been significantly affected by the operation. So there is little reason to suppose that the testes, despite showing histological evidence of hyperplasia of Leydig's cells, produced excessive amounts of œstrogen.

In Case 9 the output of œstriol, although not of œstradiol and œstrone, may have been reduced by orchidectomy. Yet, in this case, sections of several areas of the removed testis showed only hypoplastic tubules. There were practically no Leydig's cells present.

It therefore remains doubtful whether the testes produce abnormal amounts of œstrogen in the testicular feminization syndrome. If they do, our experience does not relate this production to overactivity of Leydig's cells. Further detailed studies of similar cases are required before a firm conclusion can be reached.

Hormone influences on sex differentiation in utero: Leaving aside the possibility of modifying sex differentiation of the female fœtus by administering androgens or progestogens to a pregnant woman, it has to be recognized that the formation of the secondary sex organs is normally dependent in some degree on hormones secreted by the fœtus. The pituitary and gonads may secrete hormones at a relatively early stage in development, but the adrenal cortex has the most obvious influence. This last is operating by the 14th to 16th week of intrauterine life and, if it is abnormal, can disturb the formation of those genital organs whose development is not complete at the time, i.e. the external genitalia. So, in the adrenogenital syndrome, the female fœtus has normal tubes, uterus and vagina but is born with a large phallus and fused labia. The resulting appearance is similar to that of a male fœtus with hypospadias. The fundamental error is an inherent failure in the adrenal's capacity to convert progesterone into hydrocortisone so that the output of ACTH by the fœtal anterior pituitary is not controlled. This syndrome is well known and requires no elaboration. It can readily be distinguished from hypospadias in a male because the affected individual is chromatin positive, and the excretion levels of both 17-ketosteroids and pregnanetriol are raised. In the male fœtus with hypospadias the chromatin sex is negative, and the excretion products of adrenal steroids are normal in amount.

The Treatment of Intersex

The adrenogenital syndrome is as easy to treat as it is to recognize. The administration of cortisone, in a dose controlled by the excretion of 17-ketosteroids, inhibits the output of ACTH to a normal level so that the adrenals cease their masculinizing influence. The treatment needs to be commenced as soon as possible after birth otherwise the child develops precociously and becomes more and more virile. With cortisone treatment, however, the girl's subsequent feminine development, menstruation and fertility are normal. The deformity of the external genitalia

can be corrected by removal of the phallus and incision of the membrane obstructing the entrance to the urethra and the vagina. The phallus at least should be removed at an early age lest its presence have an adverse psychological effect.

In other forms of intersex, treatment is not so easy and has to be determined for each case on its own merit. In general, however, it can be stated that an individual already conditioned to one social sex should rarely change. I have only advised altering the sex once and that in an individual brought up as a girl but who was very masculine in every aspect except for familial hypospadias. Although 'she' was happy to change her sex and way of life, the result was far from satisfactory. Since re-registering his sex, this man has had four operations for hypospadias. He is now married, coitus is ineffectual, he is sterile and his wife is a picture of frustration and misery.

If there is a doubt about sex at birth, various tests such as the chromatin pattern and laparotomy may help in the decision as to how the individual should be registered. Even these, however, can lead to mistakes and, in general, the best single guide is the state of the external sex organs. Thus a baby with XY chromosomes whose phallus is poorly developed as well as hypospadiac can never become a satisfactory male. He is probably best made neuter and brought up female, every effort being made to intensify femininity by removing cryptorchid testes and the phallus, and subsequently by administering œstrogens. This approach follows one of the basic principles laid down at the outset, namely, that femininity approaches the neuter state. It is therefore much easier to make an intersex appear female than male.

Treatment needs to be based on a wide interpretation of sex, and not on any one criterion such as chromosome counts, sex chromatin pattern, the histological appearance of the gonad, and the nature of the genital ducts. All go towards assessing the total picture but the final decision rests on the answer to the following question: Will this individual fit into the community better, and therefore be happier, as a male or a female?

Dr Alan C Stevenson (*Oxford*)

Evidence from Nuclear Sexing Relating to the Primary Sex Ratio in Man

The small excess of males in live births has long been known and many years ago the slightly higher M/F sex ratio in stillborn compared with liveborn infants was noticed. Many investigators such as Tschuprow (1915) and Ciocco (1938) have also sexed abortions. Data of this type appeared to show a remarkable rise in sex ratio in spontaneous losses occurring from the seventh month backward to the fourth or third months. The relationship with time was exponential so that starting from about 1·15 in the seventh month it had reached about 2·1 by the fourth month and estimates given for the third month were from 3·5 to 7·3. However, Wilson (1926) pointed out discrepancies between naked-eye sexing and the histological sex of gonads earlier than the 12th postmenstrual week, observers being prone to sex females as males because of the large size of the clitoris. Tietz (1948) reassessed the Carnegie collection of embryos and concluded that there was no excess mortality in males in the pre-28th compared to the post-28th-week losses. This, however, is difficult to reconcile with his data which seem to show a significant excess of males in the earlier losses (% pre-28th-week losses $52{\cdot}5 \pm 0{\cdot}6$; post-28th-week losses $50{\cdot}2 \pm 1{\cdot}3$).

Glenister (1956) published some results of nuclear sexing of embryos and Stevenson & McClarin (1957) and Bohle *et al.* (1957) showed that the nuclear sex of the fœtus and that of cells in chorionic villi were identical. This technique enables large numbers of abortions to be sexed even when the embryo itself is lost or is too macerated to permit sexing. The findings of published studies where more than 200 aborti have been sexed are set out in Table 1. The average ratio is 2·2, but if the high figures from the papers of Bohle *et al.* (1957) and Heinz (1959) are ignored there are 482 males and 340 females, a sex ratio of 1·42.

Table 1
Results of nuclear sexing of products of conceptions in pre-28th-week spontaneous abortions

Authors	*No. of concepti sexed as* *Males*	*Females*	*Sex ratio M/F*
Bohle *et al.* (1957)	470	175	2·68
Stevenson (1959)	204	152	1·34
Esposito (1958)	11	9	1·22
Klinger *et al.* (1958)	21	22	0·95
Heinz (1959)	556	169	3·3
Tricomi *et al.* (1960)	149	93	1·6
Wagner (1958)	81	45	1·8
Glenister (1956)	16	19	0·84
Total	1,508	684	2·20

One possible factor determining the large differences is that the German authors used old sections collected for routine histology and not specially fixed or stained. There is no doubt that it is unsatisfactory to determine nuclear sex in these sections relative to those specially fixed and stained. Although many hundreds of such specimens were available to me in my own work, I soon became convinced that I was consistently missing females and I abandoned the attempt. My

own 356 specially fixed and stained specimens presented many problems in sexing but were much easier to deal with and gave a much lower sex ratio than that derived from formalin-fixed tissues and routine stained sections. (For the technique used *see* Stevenson & McClarin 1957.)

The trend of sex ratio by month of abortion in published data is similar but not entirely consistent between series. The sex ratios found by Bohle *et al.* (1957) rise steadily from 1·30 in the first postmenstrual month to 4·4 in the fifth month and then fall. Heinz's (1959) data show 1·95 in the first month rising to 4·5 in the third month and a fall in later months.

The data of Stevenson (1959) and Tricomi *et al.* (1960) are from the only large series done with specially prepared material and relying on sexing of mesenchyme cells in the centre of the chorionic villi. This avoids the hazards of trying to sex the Langhan's cells where, as is clear from Fig 1, the distribution of nuclear chromatin in blobs all over the cell makes sexing very hazardous and consistent errors could arise in either direction.

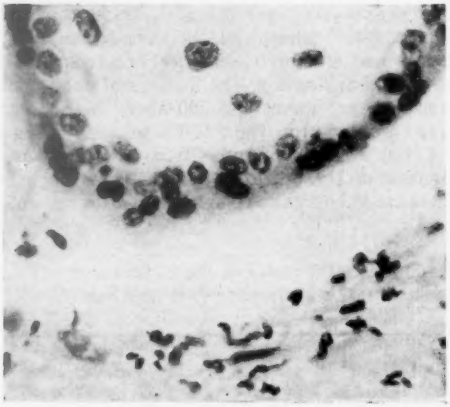

Fig 1 *From uterine scrapings, 7-week abortion. At bottom necrotic decidua infiltrated with polymorphs. Above this is seen the tip of a chorionic villus covered by Langhan's cells (cytotrophoblast). In centre of villus cells of mesenchymal origin show sex chromatin bodies*

The data by months from these two series should be reasonably comparable although there are real differences (Table 2). Although the numbers are small there is a strong suggestion that the sex ratio in the earliest recognizable abortions is less than, or not very different from, one. Nuclear sexing is on the whole easier the younger the villi. Later the mesenchyme cells disappear and tend to be replaced by Langhan's cells, but in these early villi there are plenty of good cells to sex. There should, therefore, be less chance of mistakes in sexing the early than in the later abortions.

Table 2

Distribution of products of conception examined, by postmenstrual months and nuclear sexes reported, in two series where specimens were specially collected and processed

	Stevenson (1959)			*Tricomi* et al. *(1960)*		
Month	*Males*	*Females*	*Sex ratio M/F*	*Males*	*Females*	*Sex ratio M/F*
1	15	18	0·83	3	7	0·43
2	95	70	1·36	22	13	1·69
3	63	42	1·50	72	41	1·76
4	20	17	1·18	39	24	1·62
5	7	5	1·40	10	7	1·43
6	3	0	—	0	0	—

The Sex Ratio of All Fœtuses in utero *at the End of the First Month*

Abortions early in the 'first postmenstrual month' are really those occurring about twelve or thirteen days post-implantation. For practical purposes no earlier losses are recognized and an unknown proportion occurring in the fifth and sixth postmenstrual weeks are no doubt not recognized.

In any event we want to know what numbers of conceptions by sex are present as early as possible in the uterus. The figures from Belfast for 1957 are the only data available for all livebirths, stillbirths and abortions occurring in a defined population over a period. Allowing for twin births and proportions of monozygotics and dizygotics (so that for mature births the figures are for sex ratio of concepti) and applying the sex ratio of the 356 abortions sexed to the total occurring in the year 1957 (1,127) it is possible to estimate this figure from the data in Table 3. In short, at the earliest period at which they would be recognized there are about 52% of males and of each 1,000 embryos 520 would be expected to be male and 480 female, an excess of 40 males.

Table 3

Sex of all recognized concepti where pregnancy was completed in Belfast 1957 (Stevenson *et al.* 1959)

	Males	*Females*	*Total*	*Sex ratio M/F*
Live and stillborn conceptions	4,343	4,125	8,468	1·053
Aborted conceptions	646	481	1,127	1·342
Total	4,989	4,606	9,595	1·083

Is it possible that there is an excess of female losses in the first 14 days of the life of the zygotes which would balance all the subsequent excess of males estimated to be in the uterus at the end of that period? We know that such pre-implantation and early post-implantation losses occur but are they sufficiently frequent to make it at all possible that an excess loss of females could be sufficiently large to be compatible with a sex ratio in zygotes of unity?

We know little about losses at comparable times in mammals which as a rule shed only one ovum at ovulation. Our best data in any mammal are from the mouse where, according to strain and degree of inbreeding, from 10% to 20% of zygotes may be lost at what seem to be corresponding periods (Parkes 1923, Lyon 1959). It seems unlikely that the rate in man would exceed that in a polyovulating animal like the mouse.

If 20% of all zygotes were lost in this way and there were a proportion of 52% males in all other zygotes, then to be compatible with a sex ratio of unity at conception the sex ratio of these missed zygotes would require to be 0·72. If 10% of all concepti were lost before recognition then a sex ratio of 0·47 would be required. Even 10% of all zygotes lost represents approximately the same proportion as those lost over the whole period from fourteen days post-ovulation to twenty-six weeks post-ovulation and that the number of losses in the immediate post-fourteen days period is small.

It is clearly impossible to have very strong opinions on evidence of this kind. Even if there was sufficient consistency in the graphs of sex ratio and frequency of losses by months to enable the form of a curve to be clear it would be dangerous to extrapolate backwards from such data. However, the period in which such losses must occur is small, evidence from animal breeders does not suggest more than a 10% failure of properly planned conception and there is no suggestive evidence from man that losses in this period are heavy. In view of these considerations and the need to postulate a very marked excess of female losses (a phenomenon not demonstrable for any other period of life) the *a priori* evidence suggests that the sex ratio at conception is greater than unity.

If this is so we must think in terms of gametal selection probably in spermatozoa. It is interesting to note the evidence from animals of sperm selection (Braden 1958) in respect of the short tail 'T' allele system and suggestive evidence in man in respect of sperms bearing the Y chromosome and the dominant gene for ectrodactyly (Stevenson & Jennings 1960).

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Professor P E Polani (*London*)

Sex Anomalies and Abnormalities of Sex Chromosomes

Since 1956, when it was first recognized that the chromosome number of man was 46 and not 48, and particularly since 1959, when the first chromosome anomalies were recognized in man, numerous publications have appeared on the subject. Conditions of anomalous sex development, in which previous nuclear sexing and genetic studies had already suggested the possible presence of sex-chromosome anomalies, were among the first to receive attention. Thus it was found that in chromatin-negative patients with ovarian dysgenesis the chromosome number was 45 and only a single X chromosome was present – instead of two as in normal females – whereas chromatin-positive males with Klinefelter's syndrome had a chromosome number of 47 and an XXY sex formula – the two X chromosomes of a female and the Y chromosome of a male.

The 46 chromosomes of man are represented by 23 pairs of homologous chromosomes (Fig 1). One chromosome of each pair is of paternal, the other of maternal origin and both control identical functions through their genes, though not necessarily in an identical direction. Whereas 22 pairs are morphologically identical in both males and females, the 23rd pair – the sex chromosomes – may not be so. In females the sex chromosomes are morphologically alike and are called X chromosomes. On the other hand in males there is only one X chromosome and in addition a smaller chromosome named Y. It should be remembered that during gametogenesis only one chromosome for each pair finds its way into the mature gamete – ovum or sperm – which thus contains the *haploid* chromosome number of 23. A further point needs stressing. While certain chromosomes of the human set are reasonably easily identified, others are at present more difficult to distinguish from each other. The X chromosomes are among these and the number of them that may be present can be inferred from the results of nuclear sexing. According to the nuclear sexing rule *there are as many X chromosomes in the set as there are sex-chromatin masses in oral mucosa cells plus one.*

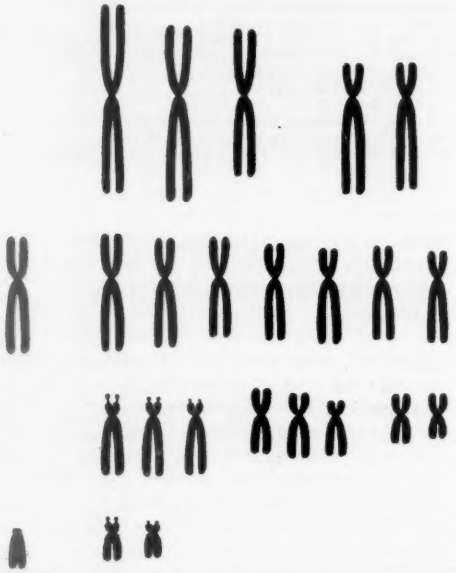

Fig 1 *Idiogram prepared from measurements of normal human chromosomes. Only one chromosome of each pair is represented together with the X and Y chromosomes on the left-hand side of the picture*

In ovarian dysgenesis with dwarfing of stature (4 ft 11 in. or under in adult life) and with or without associated anomalies, the following chromosome findings have been recorded. Most chromatin-negative subjects have 45 chromosomes and an XO sex formula. However, a few chromosome mosaics have been detected (Fig 2); *their soma is made up of two or more populations of cells with different chromosome numbers.* Patients have been described in whom cells with 45 chromosomes and XO were side by side with cells with 46 and XY: XO/XY chromosome mosaics.

SEX CHROMATIN	SEX CHROMOSOMES & CHROMOSOME NO.		
	45	46	47
—	X		
—	X	XX	
—	X	X Y	
—	X		X Y Y

Fig 2 *Schematic representation of the chromosome findings in chromatin-negative patients with ovarian dysgenesis*

SEX CHROMATIN	SEX CHROMOSOMES AND CHROMOSOME NO.		
	45	46	47
+	X	XX	
± + ++	X	XX	XXX
+ ++	X		XXX
+		XX	
+		XX	
+		X Y	

Fig 3 *Schematic representation of the chromosome findings in chromatin-positive patients with ovarian dysgenesis*

Also XO/XY and XO/XYY chromosome mosaics have been seen in this group of patients.

In chromatin-positive females with ovarian dysgenesis, two main findings (Fig 3) have been reported: (1) The presence of chromosome mosaicism, as defined above, XO/XX, XO/XXX or, even more complex, (2) the presence of a structurally altered X chromosome in addition to one normal one; in these patients the chromosome number is 46, including the morphologically abnormal X the identity of which is suspected by chromosome analysis and by the nuclear sexing results which imply the presence of two X chromosomes in the set. Mostly the chromosome interpreted as a structurally altered X chromosome has been seen to be similar to chromosome No. 3 of the human set, i.e. longer than the X and with perfectly symmetrical chromosome arms. It has been thought to represent an isochromosome (*vide infra*) made up of two long arms of the X chromosome, consequently resembling morphologically the normal chromosome No. 3. In other

SEX CHROMATIN	SEX CHROMOSOMES & CHROMOSOME NO.		
	45	46	47
−		X X	
+		X X	
±		X X	

Fig 4 *Schematic representation of the chromosome findings in patients with 'pure gonadal dysgenesis'*

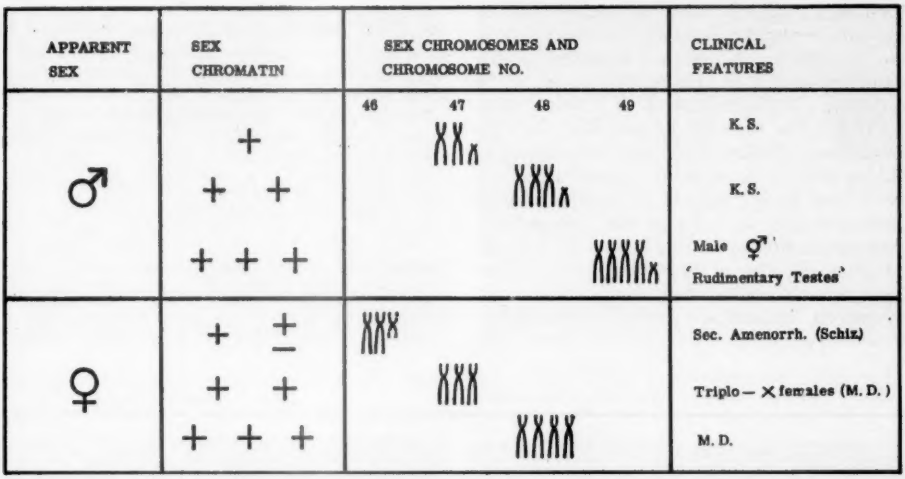

Fig 5 *Schematic representation of the chromosome findings in other patients with sex chromosome anomalies*

patients shorter and more or less asymmetrical fragments, interpreted as fragments of one X chromosome, have been seen.

In pure gonadal dysgenesis, i.e. in patients with dysgenetic ovaries without other congenital anomalies and with normal stature, an XY sex-chromosome formula has been found in the chromatin-negative subjects while an XX (or X and 'fragmented' X) complement has been seen in those who were chromatin positive (Fig 4).

Other sex-chromosome anomalies in the phenotypic females have been detected (Fig 5): triplo-X (XXX) females and also women with four X chromosomes. These patients appear generally to be sexually normal but to be mentally defective. It would appear that at least two complete X chromosomes are necessary for normal ovarian development and function, just as a normal Y chromosome is required to determine the presence of testicular tissue. The potency of the Y chromosome is sufficient to overcome the action of four X chromosomes, though the testes formed under these conditions are ever weaker in relation to the increasing number of X chromosomes in the set (Fig 5). The suggestion that the Y chromosome of man has a fundamental masculinizing role is not weakened by the few exceptions where, though a Y chromosome was present, a testis seemed to be absent or conversely testicular tissue was present in the absence of the Y chromosome. Plausible explanations, that the Y chromosome present was structurally or genically abnormal, or that gonosomic mosaicism existed or that adverse environmental forces had been active during early development, have not been ruled out in these few instances.

Origins of sex chromosome anomalies: Some may be the result of errors of chromosome partitioning in the course of one of the two (exceptionally both) reduction divisions (meiosis) of gametogenesis. Abnormal gametes, ova or sperm, may be formed without a sex chromosome or with two of them – instead of the normal one (this abnormality of behaviour is broadly termed non-disjunction). From the union of abnormal with normal gametes, individuals with one X chromosome or with three sex chromosomes (or sometimes more than three) may result. However, some of the errors, like the formation of XO females, may take place after fertilization, through loss of one sex chromosome during the earliest cell divisions of the zygote. Errors like this, occurring during cleavage of a chromosomally normal or abnormal zygote, may also give origin to the various types of chromosome mosaics through loss of a chromosome or failure of normal chromosome partitioning between two daughter cells originating from the same mother cell. Structurally altered X chromosomes, sometimes no more than fragments, might arise in various ways. They may result, for instance, if two homologous chromosomes, in one of which a segment had become inverted, were to undergo crossing-over within the inversion during the first division of gametogenesis. Inversions result from double breakage of a chromosome and 'mending' of the fragment in an inverted position within the chromosomes. Such inversions may be either paracentric or pericentric, i.e. involve the centromere of the chromosome; in this case they *may* be morphologically detectable. Finally, it is likely that some at least of the very symmetrical extra

chromosomes thought to be structurally altered X chromosomes, may be isochromosomes. These arise, also during gametogenesis in one of the parents, through a process of misdivision of the centromere. Normally this splits longitudinally separating the replicas (chromatids) of the chromosome. Under abnormal circumstances, resulting generally from the faulty movement of a chromosome during meiosis, its centromere may split transversely so that two new, symmetrical chromosomes may arise; one is made of the two short arms, the other of the two long arms, whereas, as a result of normal centromere division, each chromosome would have a long *and* a short arm.

To avoid a lengthy list of references to the various findings summarized here the reader is referred to various articles and annotations in the *Lancet*, which have appeared since April 1959 and to reviews such as those in the *British Medical Bulletin* (1961) or the Little Club Clinics in Developmental Medicine – 'Chromosomes in Medicine' (*Cereb. Palsy Bull.*, suppl. 1961, in the press).

Professor W M Davidson (*London*) read a paper entitled **Nuclear Sexing in Relation to Congenital Abnormalities**

Meeting May 26 1961

Seminar

Two Cases of Trophoblastic Disease

F E Loeffler MB FRCS, K D Bagshawe MB MRCP and Magnus Haines MD FRCOG

Mr F E Loeffler

Case 1 E H, woman aged 29, who had had one previous normal pregnancy. Her second pregnancy ended in incomplete abortion after nineteen weeks. The uterus was evacuated under anæsthesia on two occasions but no material was sent for microscopic examination. The patient then had an illness lasting twelve weeks which was characterized by persistent vaginal bleeding, respiratory complications in the form of a blood-stained pleural effusion and possible X-ray evidence of metastatic deposits in the lung fields. Diagnostic curettage produced material which had the histological appearance of chorion carcinoma (Figs 1 & 2). The Aschheim-Zondek (A–Z) test remained positive with neat urine but was negative with higher dilutions.

Case 2 J P, woman aged 29. A second pregnancy lasted twenty-one weeks and ended in spontaneous delivery of a hydatidiform mole following an intramuscular Pitocin induction. This event was accompanied by severe blood loss, hypotension and subsequent oliguria of forty-eight hours' duration. In the next ten weeks the patient remained ill with anæmia, stormy pyrexia and persistent vaginal bleeding. A chest X-ray at the end of this time showed definite metastatic deposits in the lung fields. Material removed at diagnostic curettage was reported on as 'probable hydatidiform mole'. The pathologist did not feel, however, that he could exclude chorion carcinoma (Figs 3 & 4). The A–Z test was positive with urine up to dilutions of 1/10.

Discussion: The first patient was treated by total hysterectomy with conservation of both ovaries. Examination of the operation specimen left no doubt about the diagnosis being chorion carcinoma. Cytotoxic drugs (Methotrexate and mercaptopurine) were used. The patient has done extremely well. Twenty-four-hour urine assays of F.S.H. showed normal levels of excretion. The chest X-ray returned to normal.

Case 2 received no active treatment. She has also done very well. The A–Z test became negative. The chest X-ray cleared. The retrospective diagnosis was that of 'metastasizing' hydatidiform mole. No cytotoxic drugs have been given. Had they been used a success for this form of therapy in the combat of malignant trophoblastic disease might have been claimed.

Dr K D Bagshawe

Cytotoxic Therapy

The early diagnosis of metastasizing trophoblastic tumours has been made more urgent by recent progress in cytotoxic methods. The dia-

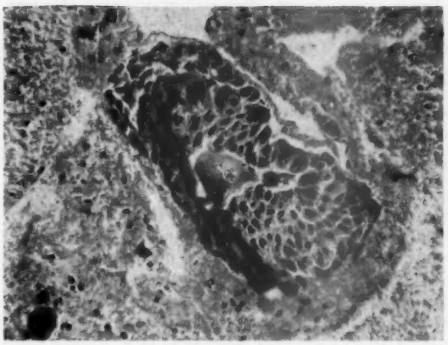

Fig 1 **Case 1** *Island of atypical trophoblastic cells. Dark-staining nuclei of irregular size.* ×165

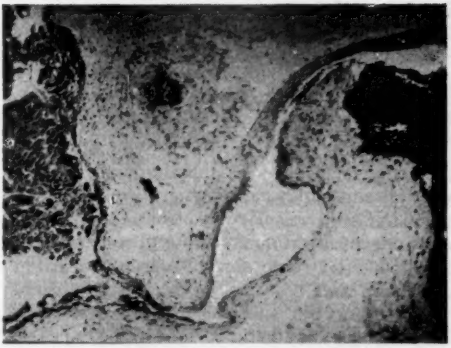

Fig 3 **Case 2** *Typical hydatidiform villus. Heaping up of trophoblastic cells on left hand side of picture.* ×40

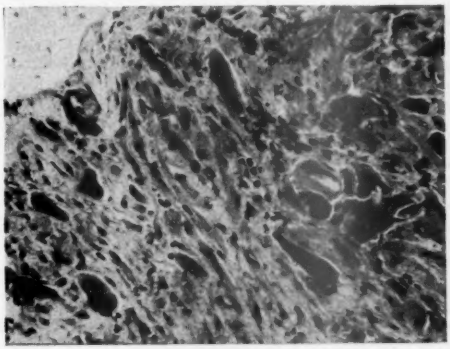

Fig 2 **Case 1** *Myometrium invaded by atypical trophoblastic cells. Some myometrial giant cells also present.* ×160

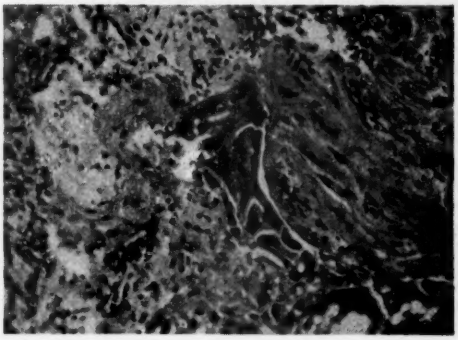

Fig 4 **Case 2** *Island of trophoblastic cells apparently invading myometrium.* ×135

gnostic difficulties are considerable but it is valuable to examine critically the case histories of such patients in the hope that delays in diagnosis can be avoided.

Case 1 had bleeding following an abortion at eighteen weeks. The possibility, however statistically remote, that such bleeding results from a tumour should be recognized when the bleeding cannot be explained by retained products of conception. Reliance on curettage alone is hazardous because the curettings are often not examined histologically and also because curettings may reveal no evidence of a tumour when one is present. Patients with heavy unexplained uterine bleeding are often discharged from hospital when they would not be discharged with similar bleeding from any other source.

If local manifestations do not lead to the diagnosis then eventually metastases will. Pleuritic pain occurring after a pregnancy should always direct attention to the possibility of trophoblastic tumour emboli causing obstruction of the pulmonary arteries even in the absence of radiological evidence of metastases. In this patient, even if there had been doubts about the malignancy of the uterine tumour, the evidence of recurrent pulmonary embolism would have justified cytotoxic therapy.

In Case 2 we have a textbook history of a patient with hydatidiform mole. The two problems subsequent to the passage of the mole were the evidence of infection and the appearance of suspicious shadows on chest X-ray. Such shadows commonly regress but the subsequent management needs to be based on clinical, radiological and hormonal assessment. Sensitive and quantitative methods of gonadotrophin assay are essential to the proper management of these patients. Cytotoxic therapy would not be warranted at this stage but if evidence of progression was obtained subsequently then this form of treatment would require consideration.

Dr Magnus Haines

Pathological Findings

In any retrospective consideration of cases of trophoblastic disease the same two points of clinico-pathological importance frequently arise, adequate laboratory examination of curetted material and biological pregnancy tests. As happened in Case 1 and possibly also in Case 2, tissue was not sent for examination until curettage was repeated, after some clinical alarm had arisen. Curettings cannot always be diagnostic in chorionic disorders but whenever material is available for histology, this should be done in the hope that a link in the chain may be available even if the first examination leaves no clue to the ultimate diagnosis. It is remarkable to find that often in fatal cases this first step was ignored. It is probable that from curettings a correct diagnosis of chorionic carcinoma is rarely obtainable. On most occasions when the suspicion of carcinoma arises histologically, it is common to find that the suspicious part of the slide can be explained as very early trophoblast or more usually as trophoblastic giant cells in muscle, endometrium or decidua (Boyd & Hamilton 1960). Another pitfall for the histologist is the chorionic carcinoma embedded in the myometrium and inaccessible to the curette.

The biological pregnancy tests are in general reliable, provided that the correct interpretation is made; it is clinical folly to rely on such tests alone. High values may be obtained in normal pregnancy and negative results have been obtained in patients dying of chorionic carcinoma. A recurring positive test, particularly if rising in titre, usually indicates malignancy.

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Mr J Stallworthy (*Oxford*) pointed out that one must not lose sight of the tremendous responsibility resting on the clinician in charge when taking decisions on which the life of a young woman might depend, and where the wrong decision might submit the patient to unnecessary surgery and lead to great unhappiness.

Dr Bagshawe and Dr Haines had referred to the difficulties in the interpretation of gonadotrophin estimations and of slides prepared from biopsy material obtained at curettage. But further difficulties might remain. The evidence might appear, both before and after operation, overwhelmingly in favour of chorion carcinoma, yet the woman might remain healthy with no evidence of recurrent trouble for the rest of her life. On the other hand the examination of an extirpated uterus might suggest that operation had been unnecessary, and yet the patient might be dead within a few months from multiple secondaries in her chest or elsewhere.

From the evidence submitted concerning the two patients Mr Stallworthy found several disquieting factors. It was a good general working principle that an empty uterus would not bleed and, conversely, if blood-stained discharge persisted following an abortion it was a reasonable inference that something had been retained within the uterus, or that there was a further complication such as carcinoma. Failure to keep constantly in mind the possibility of a chorion epithelioma following either a normal or an abnormal pregnancy, and failure to consider the possibility of a hydatidiform mole when a pregnancy was progressing in an abnormal way during the first and middle trimesters, were commonly responsible for unnecessary delay in making a correct diagnosis. Failure to consider these possibilities appeared to have been present in both these cases. Even when curettage, and a repeat curettage, had been performed in the first instance, the specimens removed were not subjected to histological examination. This omission was dangerous and could not be justified. In Mr Stallworthy's opinion the evidence in relation to Case 1, in spite of her relatively low A–Z titre, would justify a diagnosis of a chorion epithelioma and the performance of a total hysterectomy after preliminary closure of the cervix by packing and suture.

In Case 2 it was difficult to understand how the diagnosis of concealed accidental hæmorrhage could have been seriously entertained in a young woman who had been ill for several weeks, was losing weight at a considerable rate, who had noticed for herself, even if her doctor had failed to do so, that her abdomen was rapidly increasing in size, and who had obviously been an ill woman for some time prior to the occasion when she was seen in hospital. At that time her hæmoglobin was 42% and her uterus, which should have been the size of approximately a 20-week pregnancy, was the size of a 32-week pregnancy. Whether there was justification for the diagnosis of an accidental hæmorrhage (and Mr Stallworthy did not believe there was) the fact remained that it was difficult to explain why such a dangerous course of action was decided upon as to give this patient six injections intramuscularly of Pitocin without any attempt to correct the anæmia. It might be considered fortunate that she did not die during the expulsion of her hydatidiform mole, and it was not surprising, in view of the profound anæmia which then developed, that she subsequently became badly infected. Mr Stallworthy was not convinced by the X-rays that the patient had in fact secondary deposits of trophoblastic material in her chest. The Pitocin might well have been responsible for dislodging emboli, and the patient's subsequent history of recurrent rigors after evacuation of the mole could also have been associated with infective emboli reaching the lung fields.

The A–Z titre in Case 2 was low and on the evidence provided it could not be considered that this patient had a chorion epithelioma. A provisional diagnosis would be chorio-adenoma destruens, and the treatment would be to correct the anæmia, overcome the infection, and curette the uterus again if bleeding persisted. Only if the urine titre continued to rise or bleeding persisted in spite of the curettage would it be justifiable to remove the uterus.

Two Cases: Anti-Rh and Anti-Kell Antibody Production in Pregnancy

Marjorie A C Kuck MB MRCOG

Case 1 *Kell Immunization* Mrs E McC

Previous obstetric history: 1949 and 1950: Normal pregnancies resulting in live babies. 1952: Toxæmia; spontaneous labour and stillborn baby at 28 weeks. 1955: Toxæmia, spontaneous labour and stillborn baby at 28 weeks. Postpartum hæmorrhage and blood transfusion. 1957: Anti-Kell antibodies present; baby required an exchange transfusion and died age 10 hours. 1958: Anti-Kell antibodies present; intrauterine death at 28 weeks; hydropic fœtus. Husband heterozygous.

Seventh pregnancy: Anti-Kell antibodies present – albumin 1 : 32, Coombs 1 : 128. Steroid therapy commenced at 32 weeks in an attempt to diminish antibody formation.

Case 2 *Rhesus Immunization* Mrs M C

Previous obstetric history: 1956: Intrauterine death at 32 weeks; Rh antibodies present – saline 1 : 2, albumin 1 : 16, Coombs 1 : 16. 1957: No antenatal care; spontaneous labour at 34 weeks; baby hydropic. Cord blood: Hb 38%, serum bilirubin 5·4 mg%. 1959: Spontaneous labour at 30 weeks; transverse lie, prolapsed cord, internal version, breech extraction. Stillborn, apparently normal baby. Maternal blood contained Rh antibodies – saline 1 : 1, albumin 1 : 64, Coombs 1 : 128. 1960: Abortion at 9 weeks. Husband heterozygous CDe/cde.

Fifth pregnancy: Anti-Rh antibodies present: at 23 weeks, albumin was 1 : 4,000 and Coombs 1 : 8,000; at 29 weeks albumin 1 : 2,000, Coombs 1 : 4,000; at 35 weeks albumin 1 : 1,000, Coombs 1 : 2,000.

POSTSCRIPT (22.9.61): Both babies were born uneventfully and were unaffected.—M A C K

Mr D Fraser (*London*) said that he was not familiar with the Kell antigen, but presumably the patient's sensitization to this had been discovered in 1957 when she had been screened for an unusual type of immunization following stillbirth at the 28th week at her third and fourth pregnancies. He had no sympathy with a Cæsarean done as a primary procedure in her fifth pregnancy. In the sixth pregnancy he imagined that the corticosteroid therapy had been initiated to distract the reticulo-endothelial system from producing anti-Kell antibodies. He was impressed with the side-effects of such therapy which might complicate labour or operations on such patients. He noted that the husband was heterozygous Kell, and in the six pregnancy it was understood that there had been no appreciable change of antibody titre up to 37 weeks. The patient was well past her danger time at 28 weeks, and he would take the view that the baby was Kell-negative, and would await the onset of labour at term.

With regard to Case 2, it was unusual for a Rhesus-negative woman to lose her first baby from erythroblastosis. He assumed she had been sensitized by a previous blood transfusion or injection, or that a miscarriage had been forgotten and forgiven. The patient had repeated her obstetric pattern in her next pregnancy with a repeat severe affection of the fœtus at 32 weeks. Her third child was a good size for 30 weeks, and was normal to gross examination. It might have been Rhesus-negative as the husband was heterozygous. The child had suffered a traumatic delivery which was sufficient to explain its demise. The abortion in the fourth pregnancy was probably incidental, and Mr Fraser was not satisfied that Rhesus immunization was a cause of abortion. In the fifth pregnancy the patient had antibodies of fantastic intensity at 11 weeks, and the naïve view might be taken that the fœtus was either Rhesus positive or Rhesus negative. If positive it would have no chance whatever. If it was negative, and the fact that the fœtus was still alive at 37 weeks, well past the patient's usual danger time, suggested that it *was* negative, he would advise leaving the patient to come to term and await the onset of labour. The high antibody titre might have been due to an anamnestic reaction of no clinical importance.

Dr P L Mollison (*London*) said that Case 1 was typical of anti-K immunization in that it followed blood transfusion; pregnancy alone hardly ever caused the formation of anti-K. When immunization was due to blood transfusion rather than to a series of pregnancies, there was no 'selection' of homozygous husbands; thus, the chance that in the present case the father was Kk rather than KK was about 45 to 1, this being the relative frequency of the two genotypes in a random population.

The fact that the infant carried during the seventh pregnancy was K negative was suggested by the fact that it was alive and well at the 36th week of pregnancy, whereas in the previous pregnancy a K+ infant died *in utero* at about 26 weeks. The fact that the titre of anti-K was unchanged during the seventh pregnancy was slightly in favour of the same interpretation although not too much weight could be put on this since many patients showed a ceiling of antibody response and might, for example, apparently be incapable of producing a titre of more than 128 however much they were stimulated.

The influence of cortisone in a case like this was very doubtful. Experimental work suggested that the administration of steroids in ordinary therapeutic doses was unlikely to lower the antibody titre or even to interfere with a secondary response. Moreover there were many records of cases in which large doses of steroids had been given to Rh-immunized pregnant women from 14 weeks onwards without preventing stillbirth before the 28th week of pregnancy.

In Case 2, it was again significant that the fœtus was alive at 37 weeks despite the history of a previous stillbirth and of a previous infant with hydrops fœtalis, both at earlier stages of previous pregnancies. Perhaps even more significant was the fact that the fœtus was alive at 37 weeks despite the very high antibody titre

throughout pregnancy. An indirect antiglobulin titre of 1,000 to 8,000 was associated with a very high incidence of intrauterine death when the infant was Rh positive. In this case too, therefore, there was a strong indication that the infant would be normal and apart from purely obstetrical considerations should have been left *in utero* till term.

When the mother had had a previous stillbirth and there was doubt whether the present infant *in utero* was Rh positive or Rh negative, examination of amniotic fluid was sometimes helpful. In such a case the obtaining of colourless fluid about the 35th week very strongly suggested that the infant was Rh negative and this might be very valuable in deciding that labour should not be induced prematurely.

Dr A D M Jackson (*London*) agreed that in both cases the fact that the fœtus was still alive at 37 weeks probably indicated that it was unaffected and should be allowed to await spontaneous delivery.

The real problem was what to do at an earlier stage of pregnancy. In such pregnancies with a heterozygous father and a previous history of a stillborn hydropic infant the risk of another stillbirth soon after 34 weeks was nearly 80% – if the baby was affected. Since it was impossible to be sure whether the baby was affected or not there was a case for considering induction at 35 weeks or even Cæsarean section at 32 weeks, though this meant a slight risk of losing an unaffected baby through prematurity.

Mr M D Cameron (*London*) thought the most interesting point regarding Case 1 was the anæmia of the infant. The hæmoglobin at birth was 91%, with 18% reticulocytes; the serum bilirubin was 2·9 mg%. The explanation given by Dr Mollison of this being due to fœtal bleeding into the maternal circulation from a placenta traumatized by abdominal amniotic taps was most interesting. Very careful consideration should be given before performing this procedure in the future, especially as the information which could be expected from it was very limited.

Mr Leonard Easton (*London*) said that he had recently seen a case which illustrated points raised by Dr Mollison and Mr Fraser.

This woman, aged 30, was pregnant for the fifth time, the first three being normal full-term deliveries and the fourth resulting in the birth at 38 weeks of a stillborn hydrops fœtalis associated with severe congenital malformation. During her fifth pregnancy the antibody titre began high and rose steadily so that by the 32nd week the Coombs titre was positive to 1 : 2,000 and in albumin to 1 : 512. Thereafter it remained fairly steady.

Her husband was known to be heterozygous and an amniotic fluid tap at the 35th week showed 0·5 mg% of bilirubin but no oxyhæmoglobin present.

It was decided, in view of these findings, to induce labour at 37 weeks, but after surgical rupture of the membranes and a Pitocin drip, she failed to go into labour. The presentation became unstable and it was decided to deliver her by Cæsarean section. This was done forty-eight hours from the rupture of the membranes when a live male child was delivered which proved to be Rhesus negative.

Mr Easton thought that this illustrated the danger of placing too great a reliance on the antibody titre in cases where the husband was known to be heterozygous. It would seem that unless some certain method could be evolved of finding out whether the fœtus was Rhesus negative or positive it was probably better left to term.

Meeting March 24 1961

A Registrars' Clinico-pathological meeting was held, when the following specimens were shown:

Postmenopausal Bleeding Due to Secondary Deposit from a Hypernephroma of the Right Kidney in the Right Anterior Vaginal Wall
Mr D Maxwell

Rupture of Splenic Artery Aneurysm at the 37th Week of Pregnancy
Mr Ian Furler

Myoma of the Jejunum Causing Dyspareunia
Mr M R Fell

Necrotizing Enteritis in the Puerperium
Miss V M Thompson

Massive Hypertrophy of the Breasts without Lactation
Mr J C Miller

Two Cases of Vesico-uterine Fistula Following Cæsarean Section with Repair (Film)
Mr C N Hudson (for Mr W R Winterton and Mr A W Badenoch)

Chorionepithelioma of the Fallopian Tube
Mr F Cox

Cervical Fibroid Obstructing Labour in a Multipara
Mr Dennis G Bonham

Section of Otology

President J P Monkhouse FRCS

Meeting March 3 1961

Papers

On Ménière's Syndrome

by A Tumarkin FRCSEd (*Liverpool*)

Although recruitment was discovered (Fowler 1936) twenty-five years ago there is still no agreement as to its precise mechanism and I want to restate the theory that I put forward in 1950 (Tumarkin 1950), namely that recruitment occurs whenever the hair cells degenerate *from without inwards*.

To any given sound there must correspond a specific pattern not only on the basilar membrane (Fig 1) but also on the brain-stem and in the cortex. Moreover the primary cortical sensation evokes memory patterns, which determine the psychological significance of the sensation. It is generally agreed that the pitch of a sensation is determined by its position *along* the length of the basilar membrane. Just as plausibly we may say that loudness is determined by the distribution *across* the basilar membrane, for since the latter vibrates between fixed points at limbus and stria, the outermost cell will respond to minimal disturbance, the innermost cell to maximal disturbance.

Fig 2 demonstrates the importance of transverse position in relation to loudness. The innermost hair cell has a far greater loudness value than the outer hair cells in much the same way as an integer in the thousands column has a far greater value than the same integer in the hundreds, tens or units column.

Now consider a patient who has had normal bilateral hearing and has established the usual memory patterns. Suppose he develops Ménière's disease with the death of the outer cells on the right side. He becomes 75 db deaf. Now give him 100 db. He will develop a fragmentary cortical pattern. In the loudness-balancing technique we ask him to equate this fragmentary pattern with some other pattern on the healthy side. Which pattern does he choose (Fig 3)? There is only one cell working in the right – the innermost. Will he equate this arithmetically to a one-cell pattern on

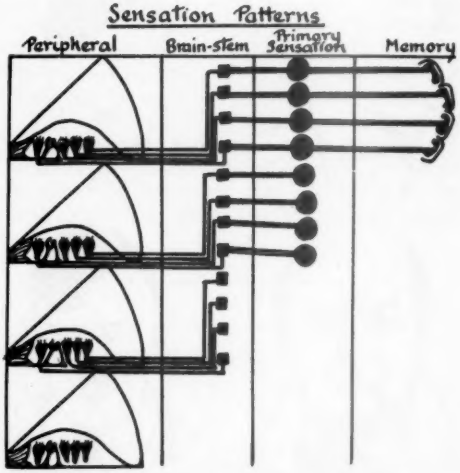

Fig 1 *Sensation patterns. A given tone activates a given cell in the organ of Corti. That cell is linked to a specific group of cells in the brain-stem and they in their turn are linked to specific cells in the cortex. The latter evoke memory patterns which determine the psychological content of the sensation*

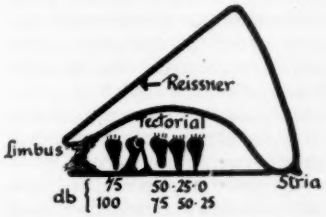

Fig 2 *Loudness is distributed across the basilar membrane. The outermost hair cell lies at the centre of the basilar membrane, i.e. at position of maximal disturbance. For simplicity the cells have been allocated arbitrary ranges: 0–25, 25–50, 50–75 and 75–100 db. Thus the innermost cell has a threshold of 75 db and reacts maximally at 100 db*

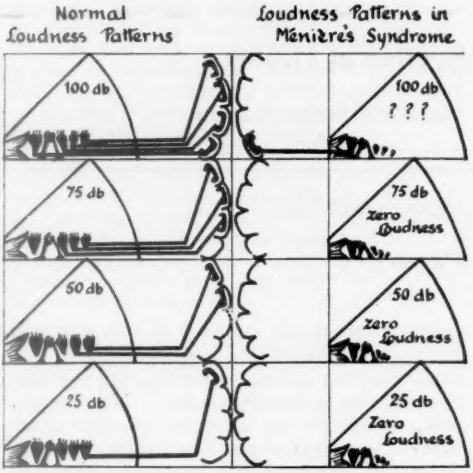

Fig 3 *This patient has lost his three outer hair cells. He is 75 db deaf. When he receives 100 db he equates this to 100 db in the normal ear, i.e. he recruits* (see *text*)

the left (i.e. the outermost)? Of course not. The innermost cell, as I have just said, has, because of its position, an intrinsic loudness value far greater than the outermost cell. In his judgment of equality the patient will be determined by a psycho-physical principle to which I drew attention in 1954 (Fig 4), namely that when the brain receives a fragmentary sensation it attributes to the fragment the 'psychological value' (in this case loudness) of the complete pattern which is suggested by the fragment – just as a few bars of music can evoke the memory patterns of a great symphony. Under normal living conditions a sound which is loud enough to stimulate the left inner cell would also stimulate the right inner cell and *vice versa*. Those two cells are 'linked' by memory patterns. Consequently in matching the isolated innermost cell of the deaf ear he must choose on the healthy side a pattern which also contains the innermost cell. But only the 100 db pattern on the left contains the innermost cell and this therefore is the pattern that he equates to the fragmentary pattern on the right. He therefore attributes to the latter a loudness of 100 db.

Thus at one leap, he passes from zero loudness, i.e. deafness, up to completely normal loudness. This is a crude type of recruitment but it is due to the crude pathology that I have postulated with total death of outer cells and a completely normal inner cell. Obviously, however, we should get a more familiar recruitment if we postulated a more gradual pathology. This then is the pattern theory – recruitment arises whenever the organ of Corti degenerates from without inwards. Such degeneration is of course not peculiar to Ménière's syndrome. Mechanical considerations suggest that the outer cells are likely to be more vulnerable than the inner and this has been confirmed experimentally. There are, however, certain special considerations that bring about this pathological pattern in Ménière's syndrome.

According to the hydrops theory some sort of osmotic process distends the endolymphatic system. The endolymph is rich in potassium and poor in sodium, thus resembling intracellular fluid. It therefore seems probable that, corresponding to the hydrops, there would be an increase in intracellular fluid – an œdema – and if so we would expect the tectorial membrane (Figs 5 and 6) to swell up and then progressively tear away from the hair cells from without inwards. Something of this kind might well be the specific pathogenesis of Ménière's syndrome.

The acid test of any theory is that it should explain known facts and it should predict unknown facts. Here are four facts: (1) The occurrence of tinnitus in Ménière's syndrome. (2) The correspondence between recuitment as tested by loudness balance and recruitment as tested by the Békésy audiometer. (3) The poor speech intelligibility in Ménière's syndrome. (4) The absence of recruitment in acoustic neuroma and similar lesions.

(1) Tinnitus: It is generally agreed that the normal hair cell bursts into action whenever its hairs are

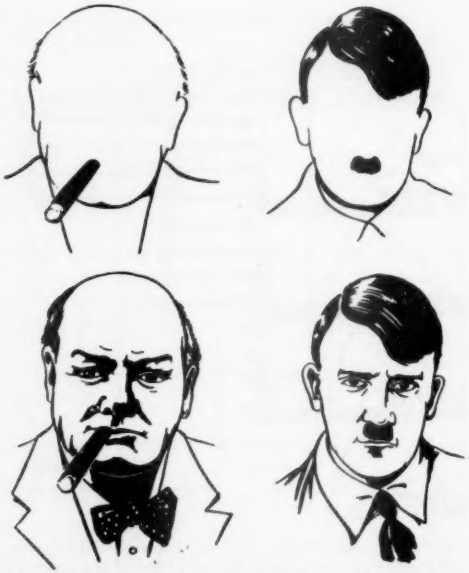

Fig 4 *A psycho-physical principle. The brain allocates to a fragmentary peripheral pattern the value of the complete central (i.e. memory) pattern that the peripheral fragment evokes*

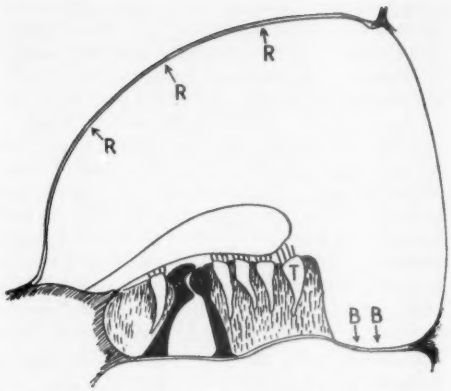

Fig 5 *Early stages in Ménière's syndrome. The endolymph accumulates and distends the scala media. Note bulging of Reissner's membrane at RR. The basilar membrane also tends to bulge down at BB. The tectorial membrane begins to swell and becomes shorter thus straining on the hair cells – more especially the outermost one T. Tinnitus and reversible deafness occur*

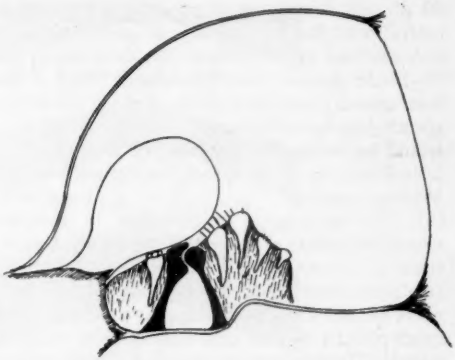

Fig 6 *Late stages in Ménière's syndrome. The tectorial membrane becomes more œdematous. It assumes a spherical shape and shortens so much that it tears away from the outer hair cells which proceed to degenerate. Irreversible deafness with recruitment occurs*
(Figs 4, 5 and 6 are reproduced from Tumarkin, 1954, by permission of the Editor of the Journal of Laryngology)

distorted by pull of the tectorial membrane. Œdema (Fig 5) will set up a continuous spurious activity resulting in tinnitus.

(2) The Békésy audiogram is essentially a discrimination test. The signal is changing both as to intensity and pitch. If a person has good discrimination he will detect those changes rapidly; if he has poor discrimination he will fluctuate much more widely. The normal ear and the conductively deafened ear appear to behave badly under this test. That is to say they fluctuate about 10 db, whereas the recruiting ear appears to behave well, the fluctuations being of the order of about 3 db. This is explained by the pattern theory as follows.

The normal ear and the conductively deafened ear at threshold listen with the outermost cell whereas the Ménière's patient is listening with one or other of the inner cells according to the severity of his deafness. But there is good reason to believe that the inner cells are more efficient discriminators than the outermost cell (Fig 7). The normal ear at threshold is a poor discriminator. It only recognizes changes of the order of 5 db whereas at higher levels it improves considerably and can detect a change of less than 1 db. At these higher levels the normal ear is using the more central hair cells, just as the Ménière's patient does at threshold. Thus the Békésy shows fine discrimination whenever the patient is listening at threshold with an *inner* cell. But we have already seen that loudness recruitment occurs for the same reason. Thus it is not surprising that the two tests give similar results.

(3) Poor speech intelligibility: When the speech is loud enough the patient records full loudness; moreover, according to the Békésy, he appears to have supernormal intensity discrimination. Why then does he fail so badly in speech audiometry? Hirsch (1952) says this is one of the most important paradoxical problems in contemporary clinical audiology.

In the pattern theory there is no paradox whatsoever. To begin with the apparent supernormal intensity discrimination is a fallacy – it is certainly no better than the performance of the normal ear *at that intensity* and it is probably rather worse. Moreover, although, owing to recruitment, the sensation appears to have normal loudness, the actual pattern in the cortex is fragmentary and mutilated. It does not yield anything like the information that the full pattern in the normal ear does. Consider the situation of a Ménière's patient who only has his innermost cells. Let us say the threshold of these cells is 75 db. Speech at

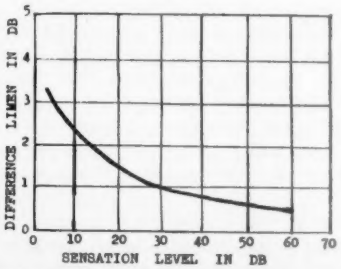

Fig 7 *Difference limen for intensity of pure tones as a function of the sensation level of the tone (after Riesz). Intensity discrimination at threshold is poor*

90 db will sound very loud to him because of recruitment. But the loudness of speech is mainly concentrated in the vowels. The consonants are 15–20 db *quieter* than the vowels. Thus if the total speech power is 90 db the consonants in that speech only have a power of 70/75 db so that they would be below the threshold of the innermost cells. Hence the poor speech intelligibility of the Ménière's patient.

(4) The absence of recruitment in acoustic neuroma is easily explained by the pattern theory, since it is most unlikely, if not impossible, for random pressure by a tumour to destroy the VIII nerve in such a regular fashion as to simulate the exact pattern of hair cell degeneration which is essential if recruitment is to occur. Thus it seems reasonable to claim that this pattern theory offers an adequate explanation for some of the most striking and characteristic features of Ménière's disease.

The Audiogram in Ménière's Syndrome

It is said that the deafness is usually unilateral. That is certainly not our experience. Over half our cases showed bilateral deafness. There are two distinct types; the low-tone loss and the high-tone loss. Of course there are many intermediate types and combinations but these two are clearly distinguishable.

The low-tone type is comparatively rare: McLay (1960) found only 8 out of a total of 124 cases. One of our groups totalling 81 included 11 with low-tone loss. All were women and their ages appeared rather lower than the average, but we are not attaching any significance to this until we have had the opportunity of studying a larger group. The most striking feature of this low-tone curve is its fluctuation. We have been so impressed by this that we nowadays include it in our prognosis. We usually promise some recovery of hearing, if only for a time.

It has been suggested that low-tone loss is an early stage which passes into the more familiar type with high-tone loss. I am certain this is not correct. The two types appear to be quite distinct and I suggest they are mediated by entirely different pathological processes. In particular I am beginning to suspect that middle-ear pathology may be the determining factor in certain types of Ménière's syndrome. For example, about half our patients have pathological tympanic membranes. Moreover their mastoids show a striking amount of hypocellularity and sclerosis. We shall do well therefore to consider by what means middle-ear pathology might damage the inner ear. Consider first the eustachian tube. This should open during every act of deglutition. Suppose the mechanism is incompetent and the tube fails to open with deglutition until quite a high intratympanic vacuum has developed.

Every abortive swallow will be accompanied by a sharp increase in the vacuum as the muscles vainly try to pull the tube open. And so there will be a pulsating vacuum periodically mounting to a peak then collapsing only to start up again immediately (Fig 8). It will suck the drum inwards, but it will also suck the round and oval windows outwards tugging directly on the perilymph of the scala tympani and vestibule. This would produce a sort of tidal flow of cerebrospinal fluid up the aqueduct of the cochlea (Fig 9) but it is by no means certain that there is a free communication between perilymph and C.S.F. If free flow does not occur along the aqueduct then the suction will be transmitted to the endolymph and this again could act in several ways. First there might be a tidal current of endolymph along the ductus endolymphaticus which could disturb the saccule and utricle. It could also suck a tide of endolymph into the scala media thus producing a hydrops from mechanical means as opposed to the osmotic action which is usually postulated.

If this endolymph tide does not occur the suction action will be transmitted by the endolymph to the cellular elements. Under suction the tectorial membrane might swell up and tear away

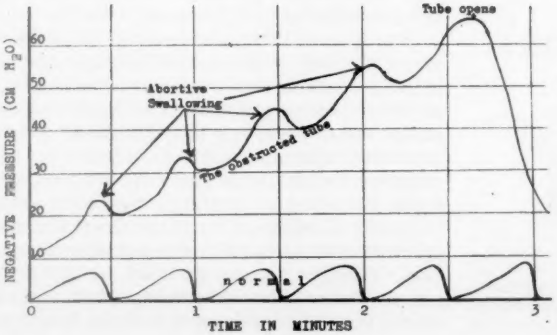

Fig 8 *Vacuum effects within the middle ear. The normal tube opens several times per minute so intratympanic pressure variations are minimal. If opening is incompetent a pulsating vacuum will develop*

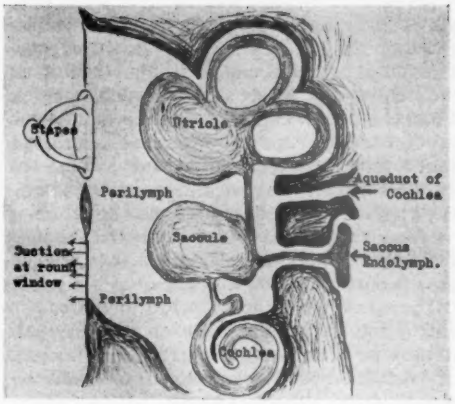

Fig 9 *Tidal flow in perilymph and endolymph. Suction at the round window drags primarily on the perilymph. If the aqueduct is impermeable the effect is transmitted to the endolymph. If this fails the effect is projected directly on to the neurocellular structures*

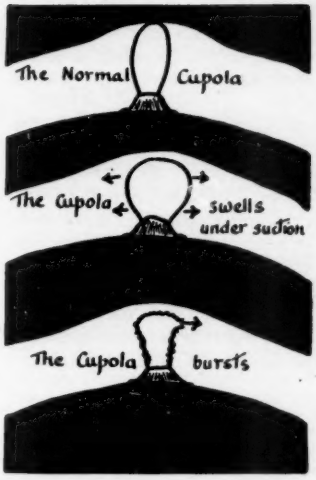

Fig 10 *The bursting cupola. The sudden onset of the attack in Ménière's syndrome might be due in some cases to rupture of the cupola from endolymphatic suction. Unsteadiness would persist until the cupola reformed*

from the hair cells. It might even rupture in places, so pouring some of its albuminous contents into the scala media as has been noticed by Dix & Hallpike (1950).

Similar suction might cause the cupola to swell and perhaps even burst (Fig 10). Such a rupture could account for the sudden violent onset of Ménière's syndrome. Lastly this vacuum effect could explain the curious low-tone deafness. Low tones are heard at the apex of the cochlea where the basilar membrane is comparatively wide and flabby and so more prone to yield under the tug of the vacuum than at the base where the high tones are heard and where the basilar membrane is more rigid and resistant. Thus it appears that if vacuum does affect the labyrinth it could produce the exact picture of Ménière's syndrome: the tinnitus, the low-tone deafness, the hydrops, the albuminous coagulum, the fluctuations, the violent onset, &c.

Now I have said that this vacuum hypothesis might account for the low-tone deafness. We must seek elsewhere for an explanation of the much commoner high-tone deafness. Can middle-ear pathology produce high-tone perceptive deafness? Why not? Fowler showed years ago that diplacousis binauralis dysharmonica quite commonly occurs in acute otitis media as a result of inflammation, spreading to the basal coil *via* the promontory, so that the effect is most pronounced in the high tones.

Šercer & Krmpotić (1958) in their study of presbyacusis describe 'hyperostotic changes which are most strongly developed in the basal coil. These close gradually the channels in the tractus spiralis foraminosis and crush the fibres passing through them'. They add, however, that 'this is not a regular process connected necessarily with ageing. It is conditioned by special local circumstances – the frequency of its development depending on the general constitution of the individual concerned'. Is it not possible – nay probable – that these 'special local circumstances' are nothing more than the tympano-mastoid sclerosis of the hypocellular bone? And if this argument holds for the high-tone perceptive deafness of presbyacusis why should it not apply to the high-tone perceptive deafness of Ménière's syndrome, especially to those cases occurring in aged artisans in whom middle-ear pathology is so frequently found.

The Endolymph Tide

As already mentioned, this would tend to occur if for any reason there was obstruction to the perilymph tide. It is not difficult to envisage precisely that effect arising from involvement of the cochlea aqueduct in this same process of hyperostosis. The duct is a very narrow channel at best. Some workers doubt whether it really is patent and maintain that there is no free communication between perilymph and C.S.F. But even if such a communication is present in the normal ear it would take comparatively little fibrosis to obliterate it and to throw the full strain of any vacuum effect on the endolymph system.

In conclusion I want to emphasize that there is no inevitable clash between the more familiar vascular theory and the views I have outlined in

this paper. Ménière's syndrome is not a simple entity with a single ætiology. Rather is it a complex of ill-defined processes, some of which arise within the middle ear, others may be neurogenic – others vasomotor and so on.

If middle-ear pathology does indeed play the important role I have ascribed to it, our quest for the basic ætiology will carry us back to the formative years of childhood – to those recurring infections of the upper respiratory tract that still undermine the health of so many of our children. Unfortunately our understanding of those diseases is still far from complete. Many fundamental problems still challenge and defy us. Not until they have been solved will it be possible to evolve a truly rational therapy for Ménière's syndrome.

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Clinical Implications of the Late J C Seymour's Work

[*Abridged*]

by T J Wilmot MS FRCS (*Omagh*)

James Seymour had the ability to think clearly, logically and physiologically about a problem, reach a theoretically sound solution, and then proceed by carefully thought out experimental procedures to prove whether he was right or wrong. He did not rush into publication, he did not neglect the work of others, he did not take short cuts, he worked out his own techniques and he used his superlatively dexterous hands, excellent eyesight and keen brain to observe the results. He did in fact seek the truth in any subject he was investigating, and it was this complete integrity and failure to compromise that make all his observations on subjects concerning our specialty of more than common interest.

Seymour was essentially a physiologist, but he was also a very shrewd clinician whose experience of neurology and neurosurgery was extensive. Although not trained in ear, nose and throat work he took a very great interest in it and, in fact, devoted the last ten years of his life to problems which concern the Sections of Laryngology and Otology.

He believed first and foremost that many head and neck disorders were primarily due to vascular changes. These could be brought about either through a humoral agency or by abnormalities of the autonomic nervous system. Comparative studies had shown him that each important organ in the body – such as the liver, the kidney, the spleen, the eye, the musculature and the skin – has a different individual micro-circulatory pattern. He felt sure that such an important structure as the inner ear must have its own pattern also, and proceeded to confirm this by his very brilliant experimental work.

The circulation of the brain, too, interested him greatly and the fact that the main arterial supply to the base of the brain also gave the sole source of oxygenated blood to the inner ear was of tremendous significance to him.

Holding such wide views, it was natural that one of his most important contributions to our specialty was in directing attention to factors which had before seemed irrelevant or unimportant. He considered that many of our E.N.T. problems were primarily autonomic dysfunctions acting through definite vascular mechanisms. Obviously, where this is possible or likely, the patient must be looked upon as a whole. Not only must the ears, nose and throat be examined – but the pulse must be felt, blood pressure recorded, peripheral circulation in the fingers and optic fundi inspected, and the patient questioned carefully in relation to nicotine consumption, alcohol intake, presence or absence of Raynaud's disease, chilblains, migraine, bronchospasm, coronary pain and other evidence of circulatory insufficiency or autonomic imbalance.

In November 1959 at a small clinical meeting held in Omagh to demonstrate the effects of applying his physiological principles in some common clinical disorders I showed him a young girl of 16. She had lost all useful hearing in one ear as the result of a sudden vascular impairment, and her other ear was progressively deteriorating – presumably from the same cause. To try to save her second ear, I had done a cervical sympathectomy with very dramatic improvement. After hearing the story and studying the audiographs, he asked her to stand up on the chair. 'Yes', he said, 'she was almost certain to have acrocyanosis with a history like that'.

In another patient, a middle-aged executive with progressive bilateral perceptive deafness and tinnitus, after taking the blood pressure and inspecting the optic fundi, he suggested examination of the blood lipids and cholesterol – which were found to be significantly above normal. Correction of the diet and a course of Lipostabil produced a remarkable improvement in his hearing and tinnitus, and a very grateful patient.

Seymour believed that the future elucidation and treatment of the causes of perceptive deafness depended upon the members of our specialty developing a greater interest in general medicine and neurology; and that unless this occurred, the whole field opening out in relation to perceptive deafness and vertigo might be taken over by other specialties. If, as also seems possible, neurosurgical techniques prove of value in the treatment of some nasal disorders, it will be appreciated that this view is not a fanciful one.

Seymour's observations on some related subjects are therefore of interest.

Migraine

Patients with this very common and distressing condition are often referred to our clinics. We know that the vasomotor centre acts largely by controlling the circulating blood all over the body by constant tonic stimulation of vasoconstrictor autonomic nerve fibres. The degree of tone, however, seems to vary widely in different individuals, or groups of individuals, and excessive tone acting through simple reflex arcs may be responsible for ischæmic effects in different parts of the body. Such ischæmia is usually followed by reactive vasodilatation and it now seems virtually certain that migraine is caused in this way. The hemicranial type of migraine is probably associated with constriction of one or other carotid system, whereas other types, and in particular those associated with occipital headache and vertigo, are due probably to spasm of the basilar artery or of one or both vertebral arteries. Basilar artery insufficiency could certainly account for some associated vertigo by producing ischæmia of the vestibular nuclei, and similar involvement of the lower visual centres might well account for the ocular manifestations. In severe basilar artery insufficiency, no doubt, the internal auditory artery itself is cut off and ischæmia of the peripheral organ added to that already present results in a typical attack of Ménière's syndrome being associated with the headache and vomiting.

Seymour was one of the first to argue that if maintenance therapy with vasodilator drugs can help patients keep free from attacks of aural vertigo – which had been his experience – then it should be possible to lower the incidence of severe migrainous attacks by the same means. This he showed to be the case in several patients who consulted him about their vertigo but also complained of severe migraine, and whom he noted to have a tendency to arterial spasm of the retinal vessels. Some of these patients found the first relief they had ever had by this form of treatment. Theoretically, it should be possible to abort an actual attack by the same treatment, and in my area of Northern Ireland several general practitioners have had most encouraging results with cases of migraine by treating the patient with an efficient vasodilator drug early in the attack.

Atrophic Rhinitis

Some five years ago, Seymour suggested to me that atrophic rhinitis might be due to sympathetic overactivity. He thought that the condition was probably due to spasm of the arterioles supplying blood to the mucosa. If this be the case, one would expect the process to affect first the most vasoactive part of the mucosa, that is, the anterior portions of the turbinates and the anterior part of the septum. I was somewhat sceptical about this until a young woman, aged 23, came to see me in 1958 with unilateral atrophic rhinitis affecting chiefly the anterior two-thirds of the mucosa. The pupil on the same side was dilated, but there was no gustatory sweating and no inner ear dysfunction. Her symptoms had been present for three years; they did not improve with conventional treatment pursued for a further year, so in 1959 I performed a cervical sympathectomy on the affected side. Her nose returned to normal within a few weeks and apart from a residual Horner's syndrome she is now sign and symptom free. Since then I have done this operation for 4 other cases of atrophic rhinitis. In one long-standing case there was no improvement – in the others marked improvement has occurred and no local treatment is now necessary.

It seems likely, therefore, that cervical sympathectomy is worth consideration in early cases of this condition. In late cases other methods of treatment are still necessary. Obviously, as in other conditions where vascular factors are involved, the time factor is of some importance, as structural damage may become irreversible.

Vasomotor Rhinitis and Nasal Polyposis

In 1951 Seymour suggested vidian nerve section for difficult cases of vasomotor rhinitis which had failed to respond to other measures. Golding-Wood (1961) and others have recently shown that relief is possible by this means, but it is not an easy operation and should not be embarked upon lightly. The results, however, do suggest that in certain cases of rhinorrhœa relative parasympathetic overactivity appears to be corrected by this procedure.

Seymour's interest in this subject continued. He noted the red, swollen turbinates which can cause nasal obstruction and discomfort after a cervical sympathectomy. Surely, however, the latter procedure would be expected to produce a pale, boggy mucosa by creating a relative parasympathetic overactivity? Obviously, even the obstructive type of vasomotor rhinitis was not due purely to such parasympathetic overactivity.

He argued that if spasm can affect the arterial end of the rich nasal turbinate blood supply, why should it not affect the venous end also? He asked me to observe what happened following a sympathetic block for a severe vasomotor rhinitis with obstruction. In certain individuals the pale lilac, swollen, inferior turbinate starts to shrink within two or three minutes, and within ten minutes there is a completely free nasal airway on the side under consideration. The mucosa becomes pink and looks normal and this persists for perhaps as long as an hour. In one of my cases the improvement has lasted for six months, but only on one side of the nose; the other has twice relapsed.

One male patient with most obstinate nasal polyposis returned to my clinic a year ago. I had removed his polypi many times. He has had courses of zinc ionization, cauterization and desensitizing injections without relief. Remembering Seymour's ideas I did a bilateral stellate ganglion block. In ten minutes, without any removal of polypi, he could breathe clearly through his nose and when he was going,he came into my consulting room and thanked me. He said his headache had gone for the first time for months and his head felt quite different. I thought he would relapse in an hour or two, but in a fortnight he was still clear and he has not required any other treatment since then.

Seymour did not advocate sympathetic block or sympathectomy as a treatment for vasomotor rhinitis, but was curious to know the post-operative state of the nasal mucosa of a patient with marked obstructive vasomotor rhinitis who underwent bilateral cervical sympathectomy for this or other reasons.

For many years Mr C P Wilson has consistently stressed the importance of autonomic harmony in the ætiology of nasal disorders, and from the above it seems clear that further research on the autonomic control of the vessels of the nasal mucosa is urgently needed. It is a great pity that Seymour cannot advise us about this and about the role of the autonomic nervous system in such other problems as intractable facial pain, epilepsy and Bell's palsy.

Seymour's Physiological Research Work on the Blood Supply of the Inner Ear and its Implications

It is important to re-emphasize that Seymour's interest in the inner ear was not confined to Ménière's disease. His interest, however, had been aroused in this subject by his early association with the late E R Garnett Passe. He saw then a great many cases of inner ear dysfunction and was fascinated, as so many of us have been, by the paroxysmal nature of the attack in a typical case of labyrinthine vertigo. When he had been personally successful in cutting short several severe attacks by the use of a sympathetic block, on the side affected, he decided that the mechanism responsible must be investigated. This simple decision cost him over ten years of constant work and has supplied us with a great many basic truths about the circulation of the blood in the labyrinth, and about the labyrinthine fluids themselves. Some of this is as yet unpublished.

His first concern was to establish the mechanism by which vascular spasm could occur. Clinically it seemed obvious that it did occur, and what is more, that it occurred most commonly in a particular type of patient, and often under stress circumstances. The association with migraine and acrocyanosis suggested that there might be an inherent tendency in some individuals for different groups of vessels to be unduly reactive to different types of stimuli. Nobody, however, had really studied the capillary fields of the labyrinth under physiological conditions, until Seymour showed in a beautiful series of experiments how this could be done. In this he received the most expert technical assistance and help from the staff of the Ferens Institute at the Middlesex Hospital.

He was able to demonstrate that the vessels of the inner ear were, in fact, far more vaso-active than had been thought and that sympathetic stimulation could reduce blood flow in the labyrinth and also reduce function. The local application of a very weak solution of adrenaline to a capillary field in the cochlea could produce the most intense vasoconstriction, which sometimes persisted for hours and sometimes resulted in permanent damage to the secreting cells of the stria vascularis. The similarity between this experimental finding in animals and the very sudden type of deafness which occurs, principally in young, normotensive and vaso-active human individuals, is striking.

If the mechanism responsible for causing such sudden and tragic deafness in a young person is the same, then very rapid diagnosis is required, combined with all the measures needed for relaxing spasm. Rest, warmth, reassurance and vasodilatation either by drugs or sympathetic block are required as emergency treatment. As some unfortunate individuals get bilateral, permanent, total perceptive deafness as a result of this condition, any case of sudden deafness, especially in a young person, must be seen without delay.

Seymour next discovered that there was a most unusual physiological mechanism within the vessels of the stria vascularis. Not only were there contractile elements at the commencement of most of the capillaries, but there was an arrangement that allowed the maximum amount of blood to get through to the vital part of the stria, when

the rest of the vessels were contracted or empty. This is what he referred to as the 'differential sparing of the strial vessels'. Although this principle had been known to apply to certain larger cerebral vessels, it had never before been described for such a small and vital organ as the cochlea. What, however, is its significance? The implication is, surely, that the labyrinthine vessels are indeed very prone to autonomic nerve impulse bombardment, but the essential secretory epithelium of the cochlea must be nourished at all costs. It is, in fact, a compensatory mechanism, and explains why hearing in an attack of aural vertigo is diminished, but seldom lost. Seymour noticed that the younger the patient with true aural vertigo, the more severe the attack, presumably again because it is only really elastic vessels which are capable of complete closure as the result of contraction. Of course repeated attacks of vascular stasis result in atrophy of the stria, with ischæmic effects upon the capillaries themselves because their physiological task of nourishing the secretory epithelium which produces the endolymph, makes them rapidly become anoxic when their own blood supply becomes inadequate. He was able to show how much thicker the wall of these capillaries is in a young person who has suffered repeated attacks of aural vertigo, than in the normal thickening process of these vessels associated with old age. This, the essential pathological feature of Ménière's syndrome, he termed 'the selective sclerosis of the stri al capillary networks'.

He also showed clearly that hydrops is a secondary effect, is associated with cochlear damage only, and can occur in the complete absence of vertigo. It is never present in the early stages of Ménière's syndrome and is due to an osmotic effect and not to raised intralabyrinthine pressure.

Seymour was against the term 'Ménière's disease' because he doubted the existence of a definite pathological entity responsible for a particular group of symptoms. He felt that these symptoms could be produced in several different ways and by involvement of different groups of vessels, and preferred the term 'Ménière's syndrome'.

If the concept of a localized vasospasm is true, an explanation at once presents itself for some of the common inner ear disorders seen in otherwise healthy subjects. Vertigo without deafness could occur by involvement of the first, or vestibular, branch of the internal auditory artery; involvement of the second branch could account for mixed vestibular and cochlear symptoms, and involvement of the terminal branch in purely cochlear symptoms. Seymour was at pains to show that, whereas the cochlea depended entirely upon the internal auditory artery, the vestibule, through its other blood supply *via* the saccus endolymphaticus, did not. Here is an explanation for progressive vascular failure, from any cause affecting the larger vessels, producing progressive perceptive deafness without vertigo.

In his neurosurgical work he had often seen patients labelled as cases of Ménière's syndrome who, on further investigation, proved to have cerebral vascular disease, basilar insufficiency, hypertension or even acoustic neurinomata. Conversely, on at least two occasions, he had seen cases admitted to the neurosurgical wards as small subarachnoid hæmorrhages, who later became clear-cut cases of Ménière's syndrome. The very fact that there is so much confusion between ourselves, the general practitioners, and the physicians as to what does, or does not, constitute a genuine case of Ménière's syndrome confirms his belief that the symptoms of deafness, tinnitus and vertigo can be caused by a variety of factors. These can vary from spasm of the precapillary sphincter mechanism in the stria vascularis to gross obstruction of a common carotid, a vertebral or the basilar artery.

If sympathetic over-stimulation can produce small vessel spasm, what evidence is there for larger vessels being affected? I well remember Seymour telling me how a man of about 40 had plunged into a wave when bathing early in the year. He disappeared but was rescued by friends who were horrified to find he had a complete hemiplegia. He was fortunate to arrive quickly at a neurosurgical centre where an angiogram confirmed the presence of complete spasm of one carotid tree, which recovered with appropriate treatment. If excessive cold can produce a spasm of such a large vessel, it is not difficult to imagine how lesser stimuli, acting on sensitive and perhaps stressful individuals, can produce the same effect in the smaller vessels.

What other parallels exist for similar excessive autonomic nerve reactions in the human body? We know that emotions can produce tears and anorexia, and that the gastric mucosa can be affected even to the extent of causing rapid ulceration. Likewise tachycardia, cardiac irregularity and perhaps even a predisposition to coronary thrombosis can occur. In similar manner the association of acute pleural effusions, ulcerative colitis, and the vestibular upsets of jet pilots with anxiety and stress seems to be more than coincidental.

If stress, acting through autonomic nervous pathways, can produce inner ear disease, we must learn how to block those pathways, temporarily or permanently, and when to block them. We must also learn to treat the whole patient.

What other factors can produce vascular insufficiency? Atheroma must play a big part in obstructive lesions – perhaps by interfering with one or both vertebral arteries, or the basilar artery itself, or by the presence of a small plaque near the orifice of the internal auditory artery, or anterior inferior cerebellar artery, or by producing an aneurysmal dilatation in a critical area.

Seymour thought that, with the unique arrangement by which the low head of pressure in the basilar artery had to feed the labyrinth *via* the long and narrow internal auditory artery, the labyrinth must be particularly prone to early ischæmic effects and that the first of these might cause tinnitus. If so, it could well be a warning symptom denoting early atherosclerosis of the cerebral vessels, and perhaps of the coronary vessels too. He thought that all such patients with idiopathic tinnitus should have their blood chemistry analysed, particularly in relation to fat content, and that the thoughtful E.N.T. consultant might be the first to direct attention to the real cause of the trouble. To illustrate the complexity and the fascination of these problems I will take the case of a woman of 55 who first consulted me in 1954 for unilateral deafness, tinnitus and vertigo of recent origin. The deafness was clearly of perceptive type but predominantly low toned. Although she had slight hypertension, the history suggested that there might be some spasm superimposed on arterial or arteriolar degeneration and I did a sympathetic block on the affected side with almost immediate improvement in hearing and cessation of tinnitus. Within a day or two her hearing had come up 60 db to normal, where it has remained, nor has she had any severe vertigo since then. By 1959 her blood pressure had risen to 200/120 but, apart from slight tinnitus and occasional slight vertigo, she was symptom free. When I saw her again a few weeks ago she looked ill, she complained of upper abdominal pain like 'indigestion', her blood pressure had fallen considerably since her previous visits, she had raised serum cholesterol and transaminase levels, and an ECG confirmed that she had had a recent coronary thrombosis. Should this not have been foreseen earlier and perhaps prevented? Obviously dietetic control and therapy in these cases will be primarily for the physician to organize, but accurate audiography will be needed to assess progress. In some cases it has already been shown that circulatory improvement and resultant improvements in hearing can result.

Although the exact ætiology of atheroma is still in doubt, the fact that sympathetic stimulation has recently been shown to have a tonic effect on the metabolism of unsaturated fatty acids, and that during acute emotional tension there is a tendency for the blood fat level to rise, seemed to Seymour to be of significance. At least we have here evidence that, in man, lipid metabolism and autonomic nervous system activity are physiologically linked. It may be, therefore, that stress can act either through alterations of blood chemistry, or directly *via* the autonomic nervous system.

We must recognize that vascular impairment of the inner ear can occur from general causes, such as anæmia, or severe debilitating illnesses – this is especially true in the very young – and also from cardiac disease or an obstructive lesion anywhere between the carotid and vertebral arteries below, and the capillaries of the stria vascularis above.

If the vascular system of a young person is involved, is it due to excessive vaso-activity, and if so, what has precipitated this? If of an older person, is it due to atheroma? Or to hypertension? Or to long-continued acoustic trauma? Or to stress?

It is clear from this that we need plenty of time to examine these patients if we are to help them.

Seymour believed that audiography, if of a high standard, is of value in the differential diagnosis of perceptive deafness. He believed that there is some correlation between the shape of the hearing curve and the lesion present. The predominantly low-tone perceptive deafness present so commonly in the younger patient with Ménière's syndrome is probably associated with capillary damage in the stria itself, and these cases are ideal for sympathectomy. When high-tone loss only is present the damage is arteriolar or further back on the vascular tree, and sympathectomy is of little or no avail, for reasons which are obvious. The intermediate cases, of course, require the greatest degree of assessment – as is true in all branches of surgery. Sympathectomy, even for the capillary group, can fail. This may be due to preganglionic fibres emerging from much higher in the spinal cord than was once thought possible. This can perhaps occur as high as the 7th or 8th cervical segment and, of course, about the level of a stellectomy. It is also possible that vasoconstrictor fibres can accompany certain of the cranial nerves.

If vertebral artery insufficiency can cause labyrinthine damage, or at least nuclear damage in the mid-brain, in the middle-aged and elderly, why should it not do so also in the very young? There has been recent evidence of a high incidence of vertebral damage in stillborn children presumably caused by birth trauma. In those who do not die, however, relative ischæmia may damage the inner ear or the vestibular and cochlear nuclei with the production of what appears to be congenital deafness.

A similar syndrome, producing inner ear effects, is 'cervical vertigo' which is, again, almost certainly due to traumatically induced vertebral artery spasm and resulting basilar insufficiency.

At the time of his death Seymour was starting to correlate his physiological material with post-mortem specimens and their relevant clinical histories, at the Ferens Institute. He had made observations on the different vessels involved in different clinical syndromes, and his interest had spread to the whole field of perceptive deafness. He was in fact, actively engaged upon the factors in common in the production of some forms of congenital deafness, of Ménière's syndrome, of sudden perceptive deafness, pre-senile deafness, presbyacusis, hypertensive deafness and the deafness associated with cerebral vascular disease. It is a tragedy that this work was cut short in its infancy.

Seymour thought that we must learn to look upon each case of deafness, tinnitus and vertigo as a challenge, and that there were not nearly enough centres in the United Kingdom where the problems of the head and neck, and especially those in connection with the inner ear, could be investigated. Teams skilled in clinical diagnosis, in the use of the auriscope, the audiometer, electro-nystagmographic equipment, the ophthalmoscope, angiography and electroencephalography are urgently required. Only by the collaboration of different specialties and the correlation of ante-mortem with post-mortem findings will the answer to many problems be found. The adoption of Seymour's basic ideas will, however, help to clarify these problems and, incidentally, will often turn a routine and perhaps rather dull E.N.T. clinic into a challenging and exciting experience.

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Venous Obstruction of the Labyrinth: Some Experimental and Anatomical Studies

by Adrian N Griffith FRCS (*London*)

Siebenmann (1894) was the first to describe the vascular supply of the labyrinth. Further investigations were carried out sixteen years later by Shambaugh (1910).

The fullest and most considered account of the vascular supply of the labyrinth is given by Nabeya (1923). He describes two routes of venous drainage in the human: the venous blood of the membranous cochlea, the saccule and the utricle drains through the inferior cochlea vein, which runs through a fine bony canal, separate but parallel to the aqueduct of the cochlea, and empties into the inferior petrosal sinus. The blood from the three ampullæ and the semicircular canals drains to the superior petrosal sinus along a vein which accompanies the aqueduct of the vestibule (Fig 1).

The venous connexion between these systems is slight. Nabeya was unable to demonstrate any drainage of venous blood from the membranous labyrinth into the veins within the internal auditory meatus, nor could he find any vascular connexions between the membranous labyrinth and its bony capsule.

From these anatomical studies it seems likely that, if the inferior cochlear vein were to become obstructed, there would be marked changes in the circulation of the membranous cochlea, the utricle and the saccule: first engorgement, then ischæmia.

The examination of the circulation in the living animal is more informative but technically much more difficult. It is a branch of physiology that has been developed and applied to the ear of the guinea-pig in a particularly elegant technique by Kimura & Perlman (1956) in Chicago.

Under intraperitoneal Nembutal anæsthesia (0·5 c.c of veterinary Nembutal/kg body weight), the inferior cochlear vein on one side is exposed with the fine dental burr, and the vein and its collaterals are widely obstructed to prevent re-anastomosis. The opposite ear is untouched and remains as a control. Whilst the vein is being obstructed, the fine vessels of the stria vascularis are observed directly and the electrical potentials of the cochlea are recorded. On recovery from anæsthesia, signs of labyrinthine disturbance are noted. Finally a series of animals were sacrificed after varying periods of experimental venous obstruction and the temporal bone prepared for detailed histological study.

Direct observation on the stria vascularis: It is possible to observe directly the blood flow within the vessels of the guinea-pig's cochlea. A tiny fenestra is made in the bone overlying the stria of the apical turn and its vessels are observed through a microscope. A cinematographic record is made, and the blood flow estimated by the comparison of the position and progress of a certain white blood corpuscle upon successive photographic frames.

Immediately the inferior cochlear vein was obstructed all vessels in the stria became dilated, and the blood flow of the strial capillaries was reduced by 90%. In one capillary there was a complete and permanent cessation of flow; in another a reduced, but still active circulation was maintained. This sudden reduction in strial blood flow, produced by the experimental lesion, continued throughout many hours of observation.

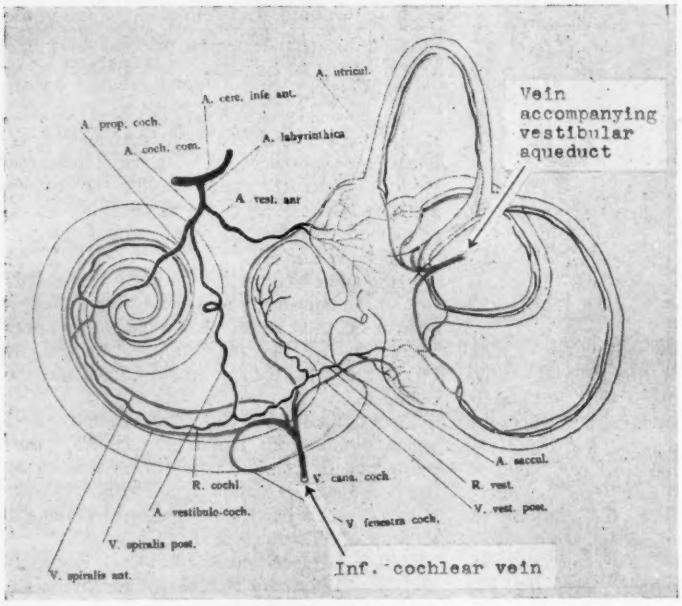

Fig 1 *Venous drainage of right membranous labyrinth viewed from the posterior medial aspect* (after *Nabeya 1923*)

There was no evidence of the rapid establishment of alternative venous drainage. No arterial spasm or vasomotor activity was observed.

Within half an hour œdema of the stria vascularis was seen. Later there was hæmorrhage into the epithelial layers and into the scala media. If the observation was continued for longer, pallor and atrophy of the stria was followed by disintegration of its surface epithelium.

Changes in the cochlear microphonics: Cochlear function was observed whilst the inferior cochlear vein was being obstructed. Cochlear microphonics and action potentials were immediately diminished and showed no recovery as long as the obstruction was maintained.

Signs of labyrinthectomy: Simple vestibular reactions were normal in all animals when tested pre-operatively. But on recovery from the anæsthetic a majority (80%) showed vestibular disturbances: a rapid horizontal nystagmus toward the unoperated ear, tilting and turning of the head and circling movements towards the operated side. These signs settled rapidly and had disappeared by the fourth day.

Histopathology of the labyrinth: The histopathological changes in 38 guinea-pigs, examined after varying periods of inferior cochlear vein obstruction, were reported in detail by Kimura & Perlman (1956) in two important papers devoted to cochlear and vestibular changes. The animals were sacrificed after unilateral venous obstruction for one, three, six, twelve hours; one two, five, seven, fourteen days; one, two, three, five, six months. In each case intravital perfusion of fixative was employed and both temporal bones were processed together with the mid-brain and cerebellum, the unoperated side being used as a control. Complete obstruction of the inferior cochlear vein that had been operated upon was confirmed in all cases.

Changes in the cochlear labyrinth: The stria and the spiral ligament appeared to be the most vulnerable parts of the membranous labyrinth. After one hour of venous obstruction the capillaries of the stria vascularis were dilated and the epithelium was œdematous; within a few hours hæmorrhage into the epithelium and the scala media had occurred. In later stages the degeneration of the stria became complete.

The spiral ligament showed rather similar changes and within six hours degeneration in the cells adjoining the external sulcus was observed and this area finally became acellular. These changes were most marked in the basal turn.

Loss of outer hair cells was clearly observed after twenty-four hours of venous obstruction; it was maximal along the basal turn. The degree varied, in some there was no visible change, in others a complete destruction. Inner hair cells were less affected, but in general small lesions were present wherever there was considerable loss of external hair cells.

The ganglion cells of the cochlea appeared more resistant and the earliest change was observed after two weeks of venous obstruction. (In one specimen an 80% loss was observed after five months).

The supporting cells of the organ of Corti, the tectorial membrane and Reissner's membrane showed slight changes only after prolonged venous obstruction for several months.

Changes in the vestibular labyrinth: In general the animal with the greatest signs of vestibular disturbance showed the greatest histological change in the vestibular end-organs. The most sensitive parts of the vestibular labyrinth were the sensory cells of the utricle and saccule. After six hours of venous obstruction pyknosis and fragmentation of the sensory cell nuclei were seen. This was followed much later by similar changes in the supporting cells. There was a varying degree of displacement of the otolithic membrane when carefully compared with the control ear. The three ampullæ showed similar changes. The sensory cells were again the first to show degeneration.

Hæmorrhage into the perilymph was conspicuous throughout the whole of the vestibular labyrinth and in some cases there was fibrosis and even ossification with obliteration of the endolymphatic space. Scarpa's ganglion and the cells of the planum semilunatum were very resistant to the vascular lesion.

Certain cautious conclusions may be drawn from these animal experiments. Functional changes take place almost immediately the vein is obstructed yet structural changes, as revealed by light microscopy, may not appear for many minutes. Irreversible changes probably do not occur within the first six hours of venous obstruction of the labyrinth.

The changes described follow sudden complete venous obstruction, where no significant collateral venous circulation is developed. But where the obstruction develops slowly, collateral venous drainage might form and the changes described would be less conspicuous. Although the early histological changes are slight, they are considered to be significant on account of the instantaneous fixation by intravital perfusion and the comparison with the control ear which was identically processed. Such precise techniques are not applicable to human material and it is unlikely that these early degenerative changes would ever be demonstrable in man.

Certain labyrinthine symptoms appear to be associated with middle-ear pathology. Temporary and often short-lived deafness, singing tinnitus, fullness of the ear, sensations of vertigo and loss of balance are often associated with a relative increase in pressure within the middle ear and there is usually a prompt relief of symptoms when the normal pressure relationships are restored. Similar symptoms may follow serous effusions and infections of the middle ear. Such pressure changes and middle-ear disease are common, but associated labyrinthine symptoms are rare. This suggests that certain individuals may be prone to them and that this tendency might depend upon an anatomical variation.

Before this suggestion is followed up some other explanations that have been put forward will be discussed.

Displacement of the stapes: It has been suggested that a change in pressure within the middle ear may displace the stapes in such a way that a current of endolymph is brought about. It is not clear whether the stapes is displaced directly or indirectly through the ossicular chain by a primary movement of the tympanic membrane. Either explanation seems improbable when experience of stapes mobilization procedures under local anæsthesia is recalled. Giddiness is not marked during manipulation of the stapes and when it does occur it is usually brought about by an unphysiological degree of inward displacement of the posterior part of the footplate.

Tympanic plexus and chorda tympani: Certain authorities have held that the chorda tympani and the tympanic plexus have anatomical connexions with the membranous labyrinth and that their stimulation within the middle ear may cause inner-ear symptoms. No convincing anatomical proof or physiological demonstration of this connexion in the human has been forthcoming and it is doubtful whether the operation of chorda tympani section or ablation of the tympanic plexus has any demonstrable effect upon the inner ear in man.

Diffusion of toxic substances into the labyrinth: In certain cases there may be a possible explanation of symptoms by the diffusion of toxic substances through the membranes of the oval and round windows. The injection of solutions of quinine into the middle ear of guinea-pigs produces the signs of a temporary unilateral labyrin-

thectomy (Hennebert & Fernandez 1959). Cochlear responses are impaired for a while and in chronic preparations postural nystagmus and abnormal turning reactions occur. Histological studies show varying degrees of necrosis within the membranous labyrinth which is maximal close to the round window. But before applying these observations to the present discussion the powerfully cytotoxic nature of this chemical must be taken into account in addition to its specific ototoxic effect. Other ototoxic drugs which are not generalized cytoplasmic poisons – salicylates, streptomycin and neomycin – may be freely applied to the middle ear without the production of any labyrinthine symptoms.

Serous otitis: A 'sympathetic' serous labyrinthitis accompanying certain middle-ear pathology has been postulated. But this finds little support in the examination of histological preparations. Even in acute otitis media, whilst a brisk inflammation is raging in the middle ear, the inner aspect of the stapes footplate and the round window show no reaction. Further, for reasons that are not yet understood, middle-ear infections complicating stapedectomy and vein graft reconstructions of the stapes rarely penetrate this thin and new formed barrier to affect the inner ear, even when infection occurs within a few days of the vein graft.

It was felt that an alternative and more probable explanation of labyrinthine symptoms associated with middle-ear pathology might lie in an anatomical anomaly of the inferior cochlear vein which would predispose to its obstruction, and it was decided to investigate the anatomy and development of this structure by examining the large number of sectioned human temporal bones in the collection of Dr J Lindsay at the University of Chicago.

Most of these specimens have been prepared for the study of pathological conditions of the labyrinth itself, and few have been cut low enough to demonstrate the whole length of the inferior cochlear vein. Serial sections of 150 human temporal bones were examined. The inferior cochlear vein in the human is formed by the union of a number of veins, the exact pattern of which is inconstant. The anterior and the posterior spiral veins of the cochlea receive a small contribution from the round window region, and are joined by anterior and posterior vestibular veins upon the infero-medial wall of the scala tympani close to the round window, where they are covered by a thin layer of bone derived from the modiolus (Fig 1). The inferior cochlear vein plunges into a fine bony canal close to the cochlear or periotic aqueduct. These two structures follow an almost parallel course each in its separate bony canal. The vein is 10 to 15 mm long and drains into the inferior petrosal sinus.

The embryological development of this region is complex but helpful in explaining the relationships and some of the anomalies. The internal ear becomes encased in a cartilaginous otic capsule between the 20 mm stage (seventh week) and the 40 mm stage (ninth week) but it is not completely enveloped, and in the early fœtus there is a cleft in the region of the cochlear fenestra between the otic capsule of the cochlea and that of

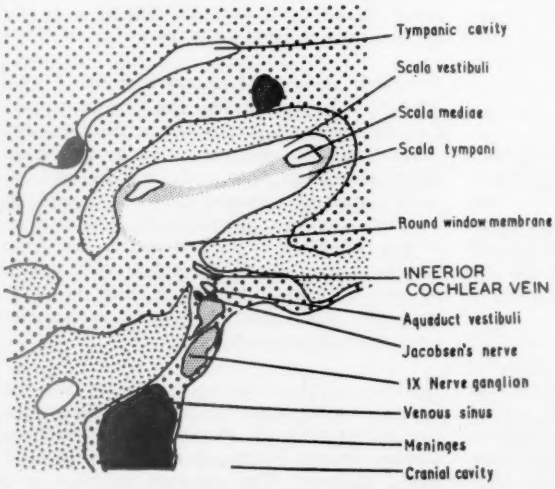

Fig 2 *Tympano-meningeal hiatus of human fœtus (62 mm)* (after *Bast & Anson 1952*)

Fig 3

the semicircular canals. This cleft, first described by Hyrtl, is known in more recent literature as the tympano-meningeal hiatus (Fig 2). It contains and contributes to several important structures (Bast & Anson 1952).

In the 40 mm stage (ninth week) the cleft is widely open, in the 62 mm stage (eleventh week) it is narrowed and by the 84 mm stage (twelfth week) the cleft is almost divided into two portions by the formation of a cartilaginous bar, derived from the region of the posterior semicircular canal. At the 100 mm stage the cartilaginous bar has fused to the otic capsule surrounding the basal turn of the cochlea and the tympano-meningeal hiatus is thereby divided into two portions. The inferomedial or meningeal part contains the aqueduct, the inferior cochlear vein and Jacobsen's nerve (which at this stage shows no glomus

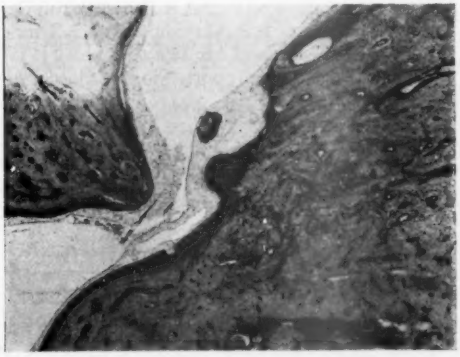

Fig 5

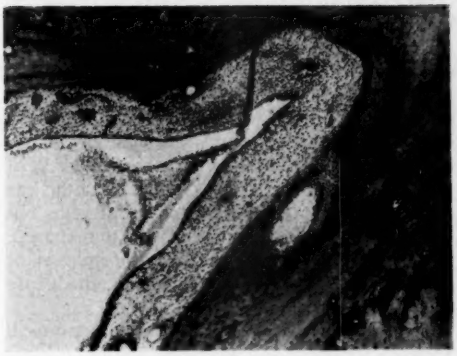

Fig 4

bodies). These structures soon become surrounded by membrane bone, so that three separate channels containing them are formed. In the fœtus this membrane bone is very conspicuous and in most adults it can be clearly distinguished from the endochondrial bone of the canalicular and the cochlear part of the labyrinth where it acts as a convenient guide to these structures.

In certain individuals this hiatus fails to close completely. A cleft of varying depth is left so that a prolongation of the middle-ear cavity enters deeply into the bony labyrinth in the region of the inferior cochlear vein. Several examples of this anomaly in the adult human were found.

The middle-ear cavity may also be brought into a close relationship with the inferior cochlear vein by the formation of deep infralabyrinthine air cells.

A number of examples were found where the party wall between the inferior cochlear vein and these air-filled extensions of the middle ear was thin and even deficient over small areas (Figs 3 & 4), and in several the inferior cochlear vein lay beneath the middle-ear mucosa in such a fashion that increase in pressure within the middle-ear cleft might bring about a total occlusion of the vein (Fig 5). The exact pressure within this vein in the human is not known, and cannot at present be measured, although it may be presumed to lie within the range of pressures attained in the middle ear during auto-inflation and sudden pressure changes associated with diving.

The exact frequency of these anomalies cannot yet be stated. Seven examples of an exposed inferior cochlear vein were found amongst 150 human temporal bones examined. If the sectioning of the region of the vein had been complete in every specimen it is anticipated that this anomaly might have been seen more frequently, and until such specimens are available it will be impossible to estimate its true frequency. During this search

other examples of interest were found. In one the inferior cochlear veins on both sides were totally absent, the entire venous drainage appearing to lie alongside the vestibular aqueduct. In another, the subject of widespread radionecrosis of the temporal bone following some years after the drinking of a 'radium water tonic', the vein lay partly exposed in the wall of the middle ear. In a case of a transverse fracture of the petrous bone the line of fracture sheared through the spiral veins but the inferior cochlear vein itself was undamaged. No example of a definite phlebothrombosis or obstruction by otosclerosis or malignant disease was found.

It is considered that, when this anatomical anomaly is present and when the inferior cochlear vein is left unprotected from pathological changes and raised pressure within the middle ear, it readily becomes occluded, and that changes similar to those described in the experimental animal will occur in the human. In certain individuals this may account for the labyrinthine symptoms that often accompany these conditions.

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DISCUSSION

Mr A B Alexander (*London*) said that Bright and Addison had published classical descriptions of diseases which were still judged to be accurate and fitting notwithstanding the necessarily limited methods of examination then available. It was only right that these diseases should continue to be linked with the names of their original authors.

Ménière's name had been used for practically every malady in otology and was still being used for a multitude of different conditions – with the notable exception of the one Ménière had described.

Ménière's disease was a fatal illness. What he had described in his classical case must have been leukæmia in which a hæmorrhage in the organ of equilibrium had occurred a few days before death.

Mr Tumarkin had suggested anew that too many different clinical entities were being included under the name of Ménière, and Mr Alexander agreed that this was undesirable. He believed that a tighter classification would be advantageous, particularly in the hope that a narrower target for scientific investigations might prove more successful than attacks on the broad front of Ménière's 'complex of affections'.

Otologists had in the past tried to impose reasoned restrictions on the use of the term Ménière: classifications put forward by individual otologists had, however, not been generally acceptable to their fellows.

Meeting February 3 1961

The following papers were read:

Problems of Tympanoplasty
Dr Dietrich Plester (*Dusseldorf*)
Experience with Pedicled Temporal Muscle Flaps in Radical Mastoid and Tympanoplasty Operations
Mr I B Thorburn
Is Myringoplasty Worth While?
Mr P H Beales

The following took part in the discussion:
Mr S R Mawson, Wing Commander P F King, Mr F McGuckin, Mr G H Livingstone, Dr I Simson Hall, Mr W Stirk Adams, Mr M P Ellis and Mr H Zalin.

The meeting will be reported in the *Journal of Laryngology*.

Meeting May 5 1961

Papers on **The Present Position of Stapes Footplate Surgery** were read by Dr Howard P House (*Los Angeles, California*) and Mr Terence Cawthorne.

The following took part in the discussion:
Mr P H Beales, Mr D W Bawtree, Mr W S McKenzie, Mr G H Livingstone, Mr Kenneth McLay, Mr R R Woods, Mr A Brownlie Smith, Mr A G Gibb, Mr S R Mawson, Mr I B Thorburn, Mr W Leach and Mr H Zalin.

The meeting will be reported in the *Journal of Laryngology*.

Book reviews

Nature of Rheumatic Heart Disease: with Special Reference to Myocardial Disease and Heart Failure
by George E Murphy MD
pp 95 illustrated 28s
Baltimore: Williams & Wilkins
London: Baillière, Tindall & Cox 1960

In this monograph the author presents his thesis for the origins of Aschoff bodies from muscle cells rather than from connective tissue. His arguments and experiments are amply supported by 162 beautifully reproduced photomicrographs. Using a specially bred stock of rabbits Murphy has most successfully produced rheumatic myocardial lesions comparable to those found in man. These 'Aschoff bodies' are convincingly shown to be the result of fragmentation of myofibres both in striated and in smooth muscle. The latter finding is new and helps to explain rheumatic lesions in sites such as the valves and atrium where connective tissue changes are usually invoked as the cause.

Clinicians will be interested in Murphy's observations on chronic rheumatic heart disease. He believes that Aschoff bodies in left atrial biopsies and in ventricular muscle signify a grade of rheumatic activity that the usual laboratory tests are too insensitive to detect. Such local myocardial lesions cause heart failure in florid acute carditis and may similarly cause myocardial failure in certain cases of chronic rheumatic heart disease.

Before abandoning the connective tissue concept, pathologists will demand histochemical support for Murphy's myogenic thesis. Moreover, recent studies have shown chemical differences between muscle fibres and Aschoff cells. Furthermore, no observations have been made in this study on rheumatic nodules, and if the existence of fibrinoid is denied in the myocardium is it acceptable at other sites? A parochial criticism of this otherwise comprehensive monograph is the absence of reference to recent British work in this field.

Highlights of Ophthalmology 1960
edited by Benjamin F Boyd MD FACS DABO
2nd ed pp xxiii+312 illustrated
Panama: 1960

The second edition of 'Highlights of Ophthalmology' follows the principles accepted in the production of the first. The book presents advances in current thinking, culled from personal interviews with outstanding teachers and from contributions to recent scientific meetings throughout the world. There is a bias in favour of ophthalmic surgery with sections devoted to instruments in ophthalmic surgery, new developments in the operating theatre, enzymatic zonulysis, advances in cataract surgery, and plastic and reconstructive surgery of the eyelids, cornea and conjunctiva. The new edition maintains the high standard set by its predecessor and is to be recommended for the library of all practising surgeons.

The author of 'Highlights' has also developed a new idea for the communication of new work in ophthalmology to his colleagues throughout the world. He has prepared recordings of the latest advances and proposes to issue such long-playing records (or magnetic tapes) at frequent intervals. The fourth disc is entirely concerned with the subject of glaucoma, and sums up the work of Chandler, Goldmann and Leydhecker in a concise and clear presentation.

The Eye and its Function
by R A Weale PhD DSc
pp 209 illustrated 55s
London: Hatton Press 1960

For the ophthalmologist accustomed to deal in great part with ocular dysfunctions, it is salutary to read the first edition of Dr Weale's book on the normal eye and its function. The striking features of his monograph are the extraordinary adaptability of the eye towards the many tasks imposed upon it in health, and the precise scientific approach of the author to the measurement of the eye's delicate achievements.

He begins with a chapter on the developing eye as an introduction, and then proceeds to describe his own field of interest in nutrition, visual pigments, the visual pathway, the retinal image, the stimulated eye, spectral sensitivity and colour vision. Each chapter is introduced by simple and fundamental observations and leads gently to the biochemical, mathematical and optical aspects of the subject under discussion. To the clinician much of the text is difficult to grasp completely, but this is no fault of the author who is tackling and explaining highly complex and integrated processes. The final chapters, on the intraocular muscles, binocular vision, the protection of the eye and the effects of some drugs, deal with the basis of everyday problems found in the ophthalmic clinic. It is a pleasure to find the two convergent approaches so well synthesized under one cover, and the book should appeal to a wide audience.

Memory, Learning and Language: The Physical Basis of Mind
University of Saskatchewan Jubilee Symposium 1959
edited by William Feindel
pp x+69 illustrated 16s
Toronto: University Press
London: Oxford University Press 1960
This book is essentially for the lay mind and attempts to introduce the various methods with which the mind can be studied by physical means.

Following a historical introduction to the theories of the Greek philosophers there is an excellent discussion of the processes of thought in relation to the structure of the brain by Dr W Feindel. This leads to an account of the psychotomimetic drugs by Dr A Hoffer and a long section on cybernetics. Finally Dr W Penfield, in a delightfully lucid chapter on aphasia, illustrates the wholly ethical way in which advances in research may be made by the clinician.

Being so short the book is necessarily sketchy and many important avenues have to be left untouched, but even so it seems a pity there is no mention of animal studies whereas an inordinate amount of space has been allocated to cybernetics, which takes up a third of the book.

Atlas of Obstetric Technic
by J Robert Willson MD MS
pp 304 illustrated 93s 6d standard edition
St. Louis: The C V Mosby Company
London: Henry Kimpton 1961
This is a new obstetric Atlas from Philadelphia. The aim is to illustrate and describe the common manœuvres of practical obstetrics and in this it succeeds extremely well. The outstanding feature is the beautifully drawn illustrations. The text is not of such high quality and unfortunately there are many omissions. For example, no mention is made of the use of ergometrine in the management of the normal third stage of labour though its use is mentioned in cases of post-partum hæmorrhage.

At a price of 93s 6d this book may prove beyond the means of students but those responsible for teaching will find it useful on account of the excellent illustrations.

A Short Textbook of Hæmatology
by R B Thompson MD FRCP
pp 306 illustrated 30s
London: Pitman Medical Publishing Co 1961
This is a clear account of disorders of the blood from the clinical standpoint which makes no attempt to describe techniques or morphological details. The arrangement is orthodox, with a brief introduction to each group of disorders followed by a survey of the clinical features, the blood changes and the treatment of individual diseases. Each chapter is followed by a short list of references, mainly to review articles or textbooks rather than to original papers in the field. Discussion of the theoretical background and of the value of newer techniques, particularly the study of cellular enzymes, is limited. The book can be highly recommended to the senior student but it is unfortunate that the recommendations of the International Committee for the standardization of the nomenclature of the blood clotting factors have not been followed.

The Anatomy of the Eye and Orbit
by Eugene Wolff
revised by R J Last MB BS FRCS
5th ed pp vii+500 illustrated £4 4s
London: H K Lewis 1961
The fifth edition of Eugene Wolff's 'Anatomy' preserves the essential form of the previous editions. As would be expected the sections dealing with the macroscopic anatomy are little changed. Most of the black and white drawings from Wolff's original preparations, which show so beautifully the relations of the oculomotor nerves and blood vessels in the orbits and cranium and which have been so largely responsible for the unique character of the book, have been retained.

The microscopic anatomy has been increasingly elaborated and some of the findings of electron microscopy have been introduced, with due cautions as to the significance of the interpretation of the observed appearances.

There are, however, some omissions, for example the minute anatomy of the trabecula and the blood supply of the optic nerve head regions, of considerable importance to the clinician and the subjects of recent research, might well have been included in this edition.

The terminology has been brought up to date. This is a most readable and authoritative edition, in which Professor Last has succeeded in capturing the spirit of the original work.

The Neural Basis of Human Behavior
by Harold Saxton Burr PHD
pp ix+261 illustrated 60s
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications 1960
The Emeritus Professor of Anatomy at Yale University aims in this book to relate changes which occur in man's behaviour with the anatomical centres which he describes within the nervous system. He writes with enthusiasm as he unfolds the physiology of the brain and the clinical features of certain disorders of cerebral function. It can be assumed from his remark that 'nearly everyone has seen at least one case of Parkinsonism amongst people they know', that this book

is not for the established physician. Indeed, it contains no original work.

The neuro-anatomical description, amplified by simple diagrams, is unusually clear and easy to read. It is a stimulating book which can be recommended to those on the fringes of neurology and psychiatry.

Carcinoma of the Colon
by Edward G Muir MS FRCS
pp vii+181 illustrated 42s
London: Edward Arnold 1961

As would be expected from a knowledge of Mr Muir's previous work, this book presents a clear, straightforward and balanced view of the subject. It can be recommended strongly to all who take an interest in carcinoma of the colon.

There are excellent chapters on pre-operative and post-operative treatment and the detail of operative treatment is shown to depend upon an accurate understanding of the anatomy of the large bowel and upon the method of spread of the disease. There is a very helpful description of anterior resection. Only one exception is allowed to the rule that no resection and anastomosis may be carried out in the face of acute obstruction. A right hemicolectomy is permitted with a side-to-side anastomosis and ileal drainage in certain circumstances for an obstructed carcinoma of the right colon.

This book can be recommended without any reservation.

New Soviet Surgical Apparatus and Instruments and their Application
edited by M G Anan'yev
translated from the Russian by John Barry Elliott
translation edited by David Brooks MD
pp x+222 illustrated 80s
Oxford, &c: Pergamon Press 1961

This book contains the proceedings of the 1st Scientific Session of the Scientific Research Institute of the Soviet Union for Experimental Surgical Apparatus and Instruments held in December 1956. The Research Institute, founded in 1951, organizes and co-ordinates technical and medical personnel. This link with engineering and other industrial facilities is well worth while since our experience in this country shows that it may take considerable time to find engineers interested in specific medical problems.

The Symposium, now unfortunately five years old, was divided into several sections dealing with a variety of subjects, ranging from a statement on the tasks for the Research Institute of the future to the problems of extracorporeal circulation.

In the lecture on basic technical stipulations, nine points were made and if all are achieved in designing any one instrument a miracle can be expected. A high if not impossible standard was set, for example: '(2) the apparatus must function infallibly under the most exacting working conditions . . . '.

Mechanical suturing appliances were given a good airing at the Symposium. These instruments are now widely used in many countries and are popular with those who use them. One section of the Symposium dealt with techniques concerned in the preservation of whole organs and limbs. In this sphere the Russians seem to be in advance of other countries. It is claimed that a simple device for perfusing kidneys in a refrigerator works satisfactorily and that kidneys can be kept perfused in this device for at least 24 hours.

It is clear from all the subjects on the agenda at this Symposium in 1956 that Russian surgery has not lagged behind other countries.

Mortuary Science
by Frederick C Gale
pp xxiii+214 illustrated 76s
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications 1961

This book which is one of the varied publications of the house of Thomas, is as usual excellently produced and illustrated. It starts with post-mortem changes (13 pages), with systems of identification (3 pages), and ends with autopsy technique (32 pages) including the 'makeshift autopsy', whilst two pages are devoted to the medico-legal autopsy. The remaining 150 pages are concerned with embalming. This is scarcely surprising as it derives from a city where up to a few years ago more than 90% of the medico-legal autopsies were conducted on already embalmed bodies. It is probably this difference in outlook which will make it of limited interest to the majority of workers in the field of legal medicine in this country who might be misled by the title.

Subnormal Personalities: Their Clinical Investigation and Assessment
by C J C Earl FRCPI DPM FBPSS
pp xiv+338 30s
London: Baillière, Tindall & Cox 1961

This book, by the late Dr Earl, has been completed by his colleague, Dr H C Gunzburg. It deals with the varieties of personality disorder seen in high-grade defectives. It consists of Earl's detailed clinical descriptions, followed by an appendix prepared by Gunzburg of the special test batteries that Earl elaborated but which, unfortunately, have never been properly standardized and extensively used.

There is sometimes a tendency to think that the study of mental deficiency is more closely akin to

pædiatrics and neuropathology than to psychiatry. Earl's work shows clearly that it is not possible to think of the mental defective as a clinical entity. The variety of personality disturbances shown are as great as in people of normal and superior intelligence, and these factors must be taken into account in any programme for the training and rehabilitation of the subnormal. This book gives a very personal account of the problems of mental defectives and some of Earl's methods may be open to criticism, but the book is of great importance to all concerned with the subnormal, in showing the importance of a proper psychiatric, as well as neurological and psychometric study of these handicapped members of society.

Assessment of the Activity of Disease
by J S Lawrence MD MRCP
pp viii+252 illustrated £2 2s
London: H K Lewis 1961
It takes a book such as this to make one realize how much it is needed. The concept of 'activity' of a disease, as opposed to its overall severity, has grown into medical thought especially in relationship to the assessment of treatment in chronic illness. The erythrocyte sedimentation rate (ESR), because of its simplicity, has been the most often used of all the numerous indices of activity and Dr Lawrence rightly devotes the majority of his space to the techniques, limitations and significance of this test.

The book also reviews diseases of the several systems of the body from the point of view of whether they elevate the sedimentation rate. This section is encyclopædic rather than informative.

The trouble is that diseases such as rheumatoid arthritis and ulcerative colitis have no identity outside the patient, and in attempting to measure them it becomes necessary to measure the patient's reaction. Two strong impressions are created. First, that 'activity of disease' is still a very nebulous concept and whatever method is used to measure activity, its limitations must be known; second, that comparison between patients will always be misleading, although serial measurement in one individual can be very helpful.

Lectures on the Scientific Basis of Medicine: Vol VIII 1958–59
British Postgraduate Medical Federation
University of London
pp ix+467 illustrated 45s
London: University of London, Athlone Press 1960
The present volume of lectures continues the excellent series. The lectures are given by men, often quite young, actively engaged in research who describe their work with, for the most part, admirable clarity.

Leukocyte Agglutinins
by Sven-Åge Killmann MD
pp 95 20s
Oxford: Blackwell Scientific Publications 1960
Interest in antibodies to leucocytes is of relatively recent origin and so far they have been studied in only a few laboratories widely scattered throughout the world. They are more difficult to demonstrate than antibodies to red cells and the techniques are exacting. The present short monograph, by an active worker in the field, is an essential reference book for all those interested in the subject. In it the author discusses critically and in detail techniques of demonstration and the properties, incidence, and significance of immune iso-agglutinins (about which there is little argument) and the more controversial auto-aggressive leucocyte agglutinins (auto-agglutinins), as well as considering the question of leucocyte antigens and the specificity of the agglutinins. From the practical point of view it seems that leucocyte immune iso-agglutinins are responsible for certain transfusion reactions and auto-agglutinin formation may be the basis of some cases of obscure leucopenia. The nature of the leucocyte-destroying mechanism in certain drug agranulocytoses remains obscure; but a rather special type of agglutinin may be involved. These and other similar problems are fully discussed.

Principles of Surgery and Surgical Nursing
by Selwyn Taylor & Olga Worrall
pp viii+290 illustrated 15s
London: The English Universities Press 1961
This book is one of a Modern Nursing Series with companion volumes in medicine, obstetrics and gynæcology, and the basic sciences, and claims to cover the requirements of the State Registration examinations. Any textbook which tries to be comprehensive in such a subject as surgery must necessarily finish up as a compromise, and in under 300 pages the authors have done well to cover the field so extensively. Although the book claims to have presented the principles of surgery and surgical nursing it tends to be a catalogue of disorders rather than of principles and their application. One doubts whether it is necessary to define such terms as Fallot's tetralogy, Klippel-Feil's syndrome and Kienböck's disease. There are very few errors – a bi-coudé catheter is illustrated as having only one bend! The format is very attractive and liberal use has been made of bold type. This is an excellent introduction to surgery for potential state-enrolled assistant nurses, but it may not provide the information which an intelligent nurse should be seeking to reinforce the information she has obtained from practical classes, lectures and ward work.